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BRITISH MEDICAL JOURNAL

LONDON SATURDAY APRIL 15 1961

A HERITAGE TO PRESERVE*

BY

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Dean of the Medical School, University of Otago

There is, I am sure, no need for me to stress the importance or the significance of this great gathering of doctors from all over the Commonwealth—the first of such magnitude to be held in this country. In preparing my address I did what I suppose most lecturers do, I looked at some of the addresses of my predecessors and read something of what had happened at previous conferences.

First Inter-Colonial Medical Conference

During my search I came across an account of the first Inter-Colonial Medical Conference held in Adelaide in 1887 at the time of Queen Victoria's Jubilee. A fascinating account of the conference appears in the first volume of the *New Zealand Medical Journal*. There were representatives from all the States of Australia, from New Zealand, and from Fiji.

His Excellency the Governor opened the conference, welcomed the visitors to "Fair Adelaide," and in the course of his remarks said: "But a few years ago a meeting of medical men engaged in the active business of their profession would have been impossible. To-day this is not only possible, but easy—thanks to the rapid improvement that has of late taken place in the means of communication between the Colonies." I wonder what he would have thought of this jet age.

You can imagine that I read the inaugural address delivered by the President with interest, and I can assure you it well repays reading. It is recorded that "he spoke eloquently for over an hour without a single note." I cannot forbear quoting some samples of his alliterative Victorian eloquence. In welcoming the guests he said: "Such a large gathering as this of busy men—some from great distances—testifies that our Congress is neither premature in time, puerile in its intentions, nor petty in its anticipated results; and we do not feel the slightest diffidence in assuming at this early period the mantle of the prophet, and predicting to those anticipations a large measure of fulfilment."

In his speech the President referred among other things to the increased risk of the introduction of disease because of the increasing speed of communication, to the need for special study of local diseases such as hydatid infection, pterygium, and Barcoo. He discussed social and climatic factors in medicine, and stressed the need for research and for the investigation of potential remedies from local plants. He referred to differences between practice in England and in Australia and suggested the need for an Australian medical journal.

After pointing out that although the journey to England "even though now contracted within the space of one month" was too long a voyage to allow of much participation in truly international conferences, he refers to the importance of local meetings. He goes on to say: "Coming as our enterprising forefathers did a three or four months' voyage over a disinfecting sea, they left many of the terrible scourges of humanity behind. The plagues of the olden time, and of the new, are largely only names and phantoms among us. Hydrophobia, the sweating sickness, relapsing fever, typhus, the cholera, have never from their shrivelled lips breathed pestilence and death over our fair land. Now and again a foul form is seen prowling at our doors: the people are anxiously uneasy at the threatening danger. But hitherto the monster has been strangled upon the threshold. I ask, is not the heritage we enjoy in our freedom from these plagues a special boon?"

Those in charge of the social programme of this meeting will have to do well to exceed the splendour of the Conversazione at the University.

"Over the entrance to the building on the outside a powerful electric light, supplied by wire from the exhibition dynamos, illuminated the grounds and greatly facilitated the movement of the numerous carriages that lined the way during the evening.

"On the main landing opposite the entrance to the library was arranged a most artistic and tastefully designed miniature fountain. This pretty contrivance consisted of a glass basin with a jet in the middle throwing up perfumed water. The basin which was lighted from beneath was surrounded by delicate ferns and foliage plants, the light shining through the crystal and making the fern leaves and other foliage almost transparent. Red camellias were placed among the leaves in such a way as to add to the effect by their brilliant colour. The whole was charming. The mechanical apparatus was worked by a tiny steam engine which obtained its power from the heat of a spirit-lamp."

Fundamental Duties in Medicine

To say that these are difficult times for our profession is merely to state what is obvious to all. This is a period of unsurpassed advance in knowledge—so rapidly

*Inaugural Address to the Biennial Conference of the New Zealand Branch of the British Medical Association and the 129th Annual Meeting of the British Medical Association, Auckland, New Zealand, February 6, 1961. Published also in the *New Zealand Medical Journal*.

acquired that no one human being can possibly keep up with it all. It is a time when the whole basis of practice is being debated and changed all over the world. Men fear domination by the State and the loss of traditional freedoms and privileges. Medical schools are concerned about the education of the doctor, and in some cases revolutionary experiments are being made. The world in which we practise is changing too—old traditions and principles are being challenged and denied. Where in this state of flux are we to seek for any stability? It seemed to me that it might be helpful for us, before we start our week of scientific sessions and social activities, to remind ourselves of some of the fundamental things in medicine—simple and commonplace but none the less important—things that, whatever else happens, we must preserve. To do this we must have a sense of history. There are certain things that have been handed down to us from the remote past—we alter them at our peril. Our own individual lives are short—pitifully short in the light of history—but while we live we have the responsibility of guarding the treasures of our heritage and handing them on unsullied and untarnished to those who shall follow us.

Whether we practise in the free enterprise system or in the Welfare State there are certain obligations and responsibilities that we must accept as a profession. At a time when men tend to think only of their privileges and the claims they can make on the rest of the community it might be salutary to think for a brief time this morning of our duties and responsibilities. I have selected eight principles which I believe are some of the fundamental duties in Medicine.

A Service for the Sick

First of all we must provide a service for those who are sick. This statement is so obvious as to be platitudinous. In these days we are so occupied with the mechanisms of disease, with the niceties of laboratory and instrumental diagnosis, and with large-scale fundamental research. W.H.O. surveys the world health situation and sets up its expert committees. Health department officials sit behind their desks and plan new hospitals and work out all sorts of statistics about the cost per bed and per square foot, and they grade doctors and assess how many house-surgeons shall be engaged for so many patients. But the real issue is much simpler than all this. John Citizen says to his wife one evening, "I don't feel well"— in New Zealand parlance, "I feel crook"—"I think I'll go down the road and see the doctor." This function of the doctor has been going on since the dawn of history. He is like the village priest going to his church and performing the duties of his office. For generations before him his predecessors have done the same, often in the same church and in the same language. So it is with us, the sick and troubled man and the doctor. This is the heart of the matter.

How is this fundamental need to be met? Traditionally it has been met by the general practitioner—the parish priest of medicine. Such a doctor normally spent his whole lifetime in one village or one suburb of a city. He knew his patients intimately—often over several generations. In this country such men were often doctors of great ability who shared all the dangers and discomforts of pioneering days. It is well that we to-day should remember them and pay tribute to them. They are part of our colonial heritage.

But to-day where do we stand? The position of the general practitioner is being examined, questioned, and challenged. One dean of a well-known American medical school said to me: "The general practitioner is an anachronism—he has gone for good."

What are the objections that have been raised to the traditional general practitioner? It is argued that it is dangerous to put one's whole trust in one man who is often overworked and tired, sometimes ill, sometimes unavailable. In these days of such rapidly increasing knowledge some people feel that no one man can know enough of medicine, surgery, obstetrics, gynaecology, and the specialties to be on his own a reliable medical adviser, and that the circumstances of his life make it difficult or impossible to keep up with new advances.

On the other hand, in the British Commonwealth, in Europe, and in the United States there has recently been a resurgence of interest in general practice, and leaders of the profession have emphasized anew its fundamental and primary importance in the community. A vigorous College of General Practitioners has been formed to push the claims of general practice, improve its status, and provide for the continuing education of the family doctor.

Perhaps we can clarify the position by asking ourselves what the average patient expects and requires and hopes for from the doctor he consults.

1. He expects to be received with kindness and courtesy. Patients will forgive lack of knowledge and mistakes in diagnosis—they seldom forgive rudeness or discourtesy.

2. He expects his doctor to be interested in what he has to say about his illness and he expects him to be a good listener. One of the fundamental complaints all through the ages is, "He wouldn't listen to me and he never examined me properly."

3. The patient expects him to know his job. Whether he does or not is difficult for the patient to assess. We know that some doctors the public think highly of have not the same standing among their colleagues. So many factors enter into success in practice. Of one thing I am sure, and that is that patients to-day do *not* as in the past expect their doctor to know the answer to every problem. If after careful investigation the doctor says to his patient, "This is a difficult problem, and I think we had better have other advice," in 99 cases out of 100 the patient's opinion of the doctor will be enhanced.

Whether a doctor treats a patient himself or gets consultant help is a matter for his own conscience. He is in the position where he himself is the sole judge of his own competence and there is no auditor.

I have heard it said that a general practitioner can himself cope with 80% of his patients. That may well be true. The important thing is that once the patient has placed his confidence in his doctor the doctor has always felt that he had a total responsibility for that patient and he would stand by him in all circumstances.

Two other things a patient expects from his doctor. The first is that he should tell him the truth—in simple language that he can understand—and the second, which is of paramount importance, is that he will respect his confidence.

I have thought a lot about this problem, and I must say I see no alternative in our day to good general practice. The conditions the patient requires will never be found in any out-patient department of the State,

however efficiently run. Neither will they be found in a collection of specialists. It requires men of the highest calibre with at least two and preferably three years' postgraduate training after qualification. It is a challenge to medical educators—especially, in my view, those responsible for postgraduate education. I regard general practice as one form of specialized practice; the training for it should be no less onerous and its status in the community should be equal to that of other specialties.

Preserving Traditional Freedoms

The second duty I would draw your attention to is the necessity of preserving traditional freedoms. We must be careful that the time-honoured rights of the doctor and his patients are not slowly and insidiously whittled away. This inevitably raises the question of the relationship of the profession to the State.

The advent of the Welfare State completely changed the position and power of the Department of Health. Previously occupied with affairs such as pure food and water, epidemiology and quarantine, it now became responsible for administering the health services of the nation. Before this the average practitioner was only vaguely aware of the department's many activities; now at every turn he ran up against the machinery of the State. Previously he was responsible only for his patient; now he was responsible to the State not only for his livelihood but also for the expenditure of vast sums of public money.

Is it any wonder there have been clashes of opinion? On the one hand, the State must safeguard public money and expenditure; on the other hand, the doctor resents the loss of traditional freedoms both for himself and for his patient. It is almost inevitable that bureaucracy will raise its irritating head.

But doctors are like all citizens and must obey the law. There is a Divine instruction that we should render unto Caesar the things that are Caesar's. There are two difficulties we face as a profession:

The first is to find out who our particular Caesar is. Sometimes he is the Department of Health, sometimes the Director-General, sometimes a committee of the Health Department; on more controversial issues, the Minister or that elusive body, Treasury. If, however, Caesar wants to put on the Royal Purple and all his panoply we find it is "the Governor-General in Council."

The second difficulty is to decide what things belong to Caesar and what do not. I do not know how much in New Testament times had to be referred to Rome, or how long it took to get a reply, but I am sometimes surprised to find how little real authority local hospital boards seem to possess and how much has to be referred to Wellington for a decision. As one who is now employed by a university, I cannot help contrasting the flexibility and wide powers enjoyed by university councils with the restrictions apparently imposed on hospital boards.

However, I am not concerned here with the local situation but with principles. The Government, through its Department of Health, has a right to expect that the profession will co-operate in all schemes for the benefit of the people, but if doctors feel strongly that the policy pursued is against the best interests of the profession or their patients, they must retain the right to express their views independently to the Government with vigour and determination.

Basic Principles of Medical Teaching

The third matter I want to refer to is the responsibility of our profession to train our successors. I am sure as we grow older we look back with increasing affection on our old teachers—those who put up with our youthful exuberance and taught us our craft and our art. It is only as we ourselves teach that we realize the extent of their patience, charity, and good humour.

A mark of our time is the amazing upsurge of interest in medical education. In almost every medical school in the world there is heart-searching and intense self-criticism in the faculty regarding the curriculum and the methods of teaching. Although perhaps this process of inquiry started in the United States, it is not limited to the North American Continent, and during a recent visit I found that some of the oldest and traditionally most conservative schools in Great Britain were actively considering major alterations to their teaching programmes.

I wish I had time to discuss this important problem of medical education—a problem that now absorbs most of my thought and energies—unfortunately there is no time. But I know most of you are aware of the efforts being made to produce a doctor who is also an educated man, to reallocate time to various subjects in the curriculum, to try to integrate the teaching of various departments, to stress the importance of learning basic principles as opposed to the stuffing with facts, and to introduce the student to social and psychological factors in disease.

What I want to stress is that teaching is not only a matter for the staff of medical schools. Every doctor should be prepared to teach and instruct his younger colleagues both in hospital and in general practice. It is one of our lifelong responsibilities. There are no tricks in our profession which one keeps up one's sleeve. It is also a two-way channel. It is the duty of the young also to instruct the old—if possible with such charm that they are unaware of the process. Let those of us who are older find our greatest joy in watching the progress of our young colleagues, and when our time comes let us retire gracefully from the scene.

Unity of the Profession

I should like now to say something about the importance of retaining the unity of the profession. With the increasing growth of specialization there is a tendency for separate and distinct groups to arise. I should be the last to decry the great advances in all branches of medicine made by intensive study of certain subjects by people who devote their whole attention to some narrow fields. But as I listen to their rather militant approach to their specialties and the claims made by some of the newer colleges and other groups I am inclined to wonder if some of them do not lack some sense of proportion and if they have read enough history. Were things really so bad before they came into existence? and, taking a long view, Are the recent advances so terribly important after all?

The important thing is that we are all doctors, and we must remember that our profession could be disrupted from within as well as defeated by pressure from without. The increasing growth of specialization makes me feel more than ever the need for good general practitioners who can look at the whole man, and, if unable to treat the patient themselves, will at least know which consultant to send him to.

Research

It is the duty of each generation of doctors to hand on to succeeding generations a better concept of the cause and nature of disease and whatever therapeutic advances it has achieved. Research in medicine is a constant duty irrespective of the system under which we practise our profession. The rate of advance has varied from generation to generation. At some periods of medical history there seem to have been long stretches of barrenness and stagnation, to be followed by exciting times of spectacular advance. Never has there been such a fruitful period as the first sixty years of this century—the times in which we have lived.

It is, of course, not possible or I believe desirable for all members of the profession to attempt research. Many have neither the inclination, the essential basic training, the time, nor the aptitude. Research requires a certain attitude of mind. There is, however, an increasing amount of good research going on throughout this country at the present time, and as more and more young men come back with good overseas training the volume of work will increase.

It has been pointed out that in New Zealand the amount spent on medical research, although increased in recent years, is a small sum compared with the amount spent on curative medicine and substantially less in proportion to our national income than in most other civilized countries. Our hospitals have on the whole been well equipped and high standards of medical care have been possible. A hospital, however, is incomplete unless it serves also the purposes of medical education and medical research. So far hospital boards, however enlightened and however enthusiastic they may be, have not been allowed to spend money to further research in the institutions they control. It is impossible to separate good patient care from teaching and research. The Director-General, I know, is aware of this fact and is sympathetic to a reappraisal of the situation. The growth of local research foundations with lay support is an encouraging feature in this country.

International Aspects

When we look back on the history of our profession it is impossible for us to hold any narrow nationalistic views. We are the heirs of all the ages and debtors to all men—Greeks, Romans, Arabs, Egyptians, and indeed every country in the civilized world. Even some of our greatest Englishmen, such as Harvey and Linacre, received their medical education in Europe, at Padua and other famous mediaeval universities. Let us remember that medicine is international. When doctors travel the world they nearly always find a welcome in another doctor's home, whatever his language or the colour of his skin.

In this suspicious, bitter, war-weary world this brotherhood of medicine is of great significance and there is probably no profession in the world, even including the Church, which is doing more for peace and understanding between nations. This is one of the fundamental glories of our profession. Sir Arthur Porritt referred at length to this problem in his Presidential Oration, "Commonwealth and Common Health," and Sir Douglas Robb is going to deal with the Commonwealth and medicine in his Presidential Oration this evening.

It is our solemn duty to do what we can to help with the medical education of less privileged countries both within and without the Commonwealth. At our own medical school we are doing our best and we hope to do more, but we are only touching the fringe of the problem.

Prevention of Disease

There is another responsibility of our profession, and that is to advise the nation and our fellow countrymen and patients on the prevention of disease and the preservation of health. Of course, departments of health will carry on with their accustomed roles of dealing with epidemic and environmental disease, but such diseases are now fairly well controlled. In spite of the great advances in our knowledge of the causation of many diseases there are still enormous gaps in our knowledge. Supposing a young man came to your surgery and said, "I want to live as long as I can and be as healthy as I can; what should I do?" The advice you could give him would be little different from what Hippocrates might have given him.

I imagine you would say something like this. "How long you live and what diseases you may acquire are to some extent genetically determined, and in the present state of our knowledge there is little or nothing we can do about this. Life is in any case uncertain, and in the world you live in accidental death is always possible and all mankind might disappear in one violent cataclysmic atomic explosion. In any case, mere prolongation of life by a few years is not necessarily very important. The quality of life is more important than its length."

What would you advise him? In the light of present knowledge you would certainly advise him not to smoke; you would give him some general advice on diet, with special stress on keeping his youthful weight throughout his lifetime; you would probably advise the cutting down of animal fats. You would certainly stress the importance of regular daily exercise and adequate vacations spent in the open air. You might well discuss with him the importance of an adequate philosophy of life. Stress and strain and worry are inseparable from life itself. Health is bound up with the way one reacts to life's difficulties and problems. The human body is not at its best when pampered and coddled. Finally, you will explain that, from now on, health is something that has to be earned by individual effort, self-discipline, and character, and cannot be bestowed by social security or an Act of Parliament. You prescribe no wonder drugs, no vitamin capsules, no magic hormones—and your young man, like Naaman the Syrian told to wash in the river Jordan, will go out into the night sorrowful and disappointed.

Medical Ethics

Finally, whatever the system of medical practice there will always be what we call medical ethics. From the time of Hippocrates with his famous Oath various codes of behaviour have been enjoined on members of the profession. I have not a great deal of faith in any particular set of rules. A man may never be brought before the ethical committee and yet his life and practice may not bring honour to our profession. The heart of the matter is that it is profoundly important what sort of a man practises medicine. In the early days of this country there were many men who often in isolated and lonely places displayed all the best characteristics of our profession.

I have just been on vacation at the central Otago town of Queenstown, set beside its lovely lake and surrounded

by its lofty hills and majestic mountain peaks. It is 101 years ago since Rees, the first settler, came to Queenstown—in February, 1860. In 1861 gold was first discovered in Otago at Gabriel's Gully, and the year following, 1862, there was a rich find near Queenstown, first of all in the Arrow River and later in the Shotover and its tributaries. By December, 1862, there were over 4,000 miners in the Queenstown area. Those of you who have visited this region can in imagination conjure up the scene. The gold was found in and on the banks of turbulent streams in deep rocky chasms with steep precipitous sides. It was impossible to construct roads round those towering cliffs of stone. In summer the miners were blistered by a pitiless sun and in winter they faced ice and snow and flood. They lived in thin calico tents or sod huts or in caves in the rock. Most of them were young and adventurous and tough. But you can imagine the insanitary surroundings, the insufficient and inadequate diet, the plagues of flies. Many died of disease, especially typhoid and diphtheria; many suffered from scurvy and frostbite; and many perished in the dreadful winter of 1863 with its terribly low temperatures and devastating floods. Accidents, many severe, were common and drunkenness was rife.

A hundred years later, as I walked over this country and thought about it, I could not help wondering if there had been any doctor there then. I made it my business to find out. There was, and I am indebted to the late Dr. Fulton for my information. A young Scottish doctor aged 25 arrived in Queenstown in 1862, just before the gold rush. There was at that time no hospital, and his consulting-room was a tent. In all weathers, by day and by night, he rode away into this dreadful mountainous country, tramped up these dark and sinister gorges—often taking his life in his hands, serving these tough adventurers. In the summer sun and in the bitterness of winter he stood beside them and served them. A lesser man would have joined them and become a miner—he knew many were making £200 a week. Some of his profession did. He never deviated from his duty. No doubt some grateful patients paid him handsomely, but it is equally certain that many never paid him at all. He was made a Justice of the Peace and had to combine his medical duties with attempts to preserve law and order in his unruly community.

In 1864 he was made first superintendent of the newly erected District Hospital and continued in that office till 1910. He died in 1911 at the age of 73. After the gold rush he became the principal doctor in the district and a public-spirited citizen. Besides being medical superintendent he was a member of the County Council, President of the Jockey Club, President of the Acclimatization Society, and a patron of the tennis and cricket clubs. His local paper said of him when he died: "During the whole of his professional career Dr. Douglas exercised the greatest medical and surgical skill and performed his duties with much assiduity. Many, many times has the old man ridden in the darkness of the night over the most dangerous and precipitous bridle tracks, into gullies and ravines amidst our gigantic mountains, in prosecution of his profession, knowing full well he would never receive a fee."

Such lives can, I know, be duplicated in the pioneering records of most countries. He would be amazed that I should think his life important enough to describe it to this audience. But in his life he exemplified the enduring qualities of our profession—a living example of medical ethics. Of such men we in this country are justly proud. Those of you from the United Kingdom can also be proud because you sent him and many more like him to us. And those of you who come from Scotland can be proudest of all because, although born in England, he was of Scottish family and was trained in Glasgow. "By their fruits ye shall know them."

AETIOLOGY OF CENTRAL NERVOUS SYSTEM INFECTIONS DURING PREVALENCE OF POLIOVIRUS AND COXSACKIE VIRUS

SOME CLINICAL MANIFESTATIONS OF COXSACKIE VIRUS INFECTIONS*

BY

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Until recently polioviruses were held responsible for the majority of infections of the central nervous system. They are, however, part of the large enterovirus group which includes also the Coxsackie and Echo viruses, and most members of this group are now recognized as being capable of causing such infections. During 1959 and 1960 virological investigations were carried out on specimens submitted to this laboratory from cases diagnosed clinically as paralytic poliomyelitis, aseptic meningitis, and encephalitis or meningoencephalitis. The findings illustrate the multiplicity of causative agents concerned in these conditions. The commonest during 1959 was poliovirus type 1, whereas in 1960 there was a striking increase in the incidence of Coxsackie virus infection, in particular types B5 and B2. The Coxsackie group B viruses are established causes of epidemic pleurodynia, aseptic meningitis, and neonatal myocarditis, but their full clinical potentialities are still being elucidated. A number of unusual clinical features, including the occurrence of paralysis, are described.

Laboratory Investigations

Virus Isolation

Faecal specimens were obtained from all patients, usually during the first or second day after admission to hospital. These were dealt with at once or kept at −70° C. for 24 to 48 hours. A 20% suspension was prepared with Hanks's solution containing 500 units of penicillin, 200 μg. of streptomycin, and 50 μg. of nystatin per ml. This was centrifuged at 4,000 r.p.m. for 30 minutes. Six tubes, comprising 2 HeLa, 2 human primary amnion, and 2 rhesus-monkey-kidney-tissue cultures, were inoculated with 0.2 ml. each of the supernatant. These were incubated at 37° C. for two hours, and the fluid of each tube was then replaced with fresh medium. The tubes were examined microscopically for cytopathic changes daily for 14 days. In positive cases the fluid was removed and the virus identified by neutralization tests, carried out usually in the type of tissue culture in which it was isolated.

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The virus was diluted 1 in 100 and mixed with equal volumes of antiserum for each of the three types of poliovirus, a pool containing all three polio antisera and a pool of antisera for Coxsackie viruses types B1 to B5 and A9. The antisera were prepared by hyperimmunization of rabbits, and each serum was used at a dilution equivalent to 20 antibody units per 0.1 ml. The mixtures were kept at 37° C. for two hours and 0.2 ml. of each was inoculated into tissue culture tubes. A virus titration was included with each test. The results were read when the control tubes showed 4-plus degeneration, usually within two to three days. When the results were equivocal because of excess virus the test was repeated using approximately 100 TCD50. Viruses which were neutralized only by the Coxsackie antiserum pool were further examined against the individual Coxsackie antisera. Those virus isolates which were not neutralized by either the polio or the Coxsackie sera were tested in the same way against Echo virus antisera types 1 to 20.

Less than 5% of the faecal specimens contained bacterial organisms resistant to penicillin and streptomycin, and these were repeated in the presence of neomycin. A very occasional specimen resisted even this treatment and was filtered through a gradocol membrane.

Destruction of tissue-culture cells within 24 hours by toxic faeces was uncommon when the replacement technique of inoculation was used, and rarely involved all three types of tissue-culture cells. When it occurred either a further specimen of faeces was obtained or a blind passage of the damaged cells was carried out.

The monkey-kidney cells were maintained on medium 199 containing SV_5 antiserum, the HeLa and amnion cells on Earle's saline containing 0.5% lactalbumin hydrolysate and 5% inactivated horse serum. Refeeding of the tubes was carried out at intervals of about five days. All tubes were incubated without rotation.

Sensitivity of Virus Isolation

Monkey-kidney, primary human amnion, and HeLa cells were of equal sensitivity for the isolation of polioviruses. In every case of isolation all three types of cell gave virus growth, but in many cases cytopathic changes occurred 24 to 48 hours earlier in monkey kidney than in amnion or HeLa cells. In a few instances degenerative changes appeared earlier in the latter tissues.

The Coxsackie group B viruses also grew in all three types of cells, but again cytopathic changes in monkey kidney were often in advance of those in either amnion or HeLa cells. This was especially marked in the case of type B2; in about half of the cases HeLa-cell isolation took three to five days longer than in monkey kidney.

Coxsackie type A9 was readily isolated in both monkey kidney and amnion but not on HeLa cells and the Echo viruses only in monkey kidney.

Serological Examinations

Sera were obtained from patients during the acute and convalescent stages of illness and were stored at −20° C. until used. They were inactivated at 56° C. for half an hour, and both sera from each patient were usually tested at the same time. All sera were examined by complement fixation for antibodies against mumps (V and S antigens) lymphocytic choriomeningitis, herpes simplex, and adenoviruses. Neutralization tests were used for the detection of antibodies against polio, Coxsackie, and Echo viruses. These were carried out by mixing equal volumes of several dilutions of each serum and virus suspensions containing approximately 100 TCD50 per 0.1 ml. They were kept at 37° C. for two hours, and 0.2 ml. of each mixture was inoculated into tissue-culture tubes. The results were read when control virus tubes showed 4-plus degeneration, usually within three to four days. Antibody titres are expressed as the reciprocal of the highest initial dilution of serum producing complete virus neutralization.

Current infection was considered to have occurred only if a fourfold or greater increase in C.F. or neutralizing antibody was demonstrable during the course of illness. In mumps meningitis, however, a V antibody titre of 256 or more associated with an S antibody titre of 64 or more in a single convalescent serum was usually regarded as significant.

Results

Virus Aetiology of Central Nervous System Infections

During 1959.—All the patients with paralysis were clinically diagnosed as cases of paralytic poliomyelitis. As will be seen, this was confirmed virologically in most but not all the cases. Cases described by the physician as aseptic meningitis and non-paralytic poliomyelitis are clinically indistinguishable and therefore only the former term is used. Stool specimens were received from 62 cases of paralytic disease. Viruses were isolated from 53 (84%) (see accompanying Table). These consisted of 52 type 1 and one type 3 polioviruses. Stool specimens were received from 93 cases of aseptic meningitis. Viruses were isolated from 26 (31%). These comprised 18 type 1 and one type 3 polioviruses, five Coxsackie type B4 viruses, and two Echo viruses, types 3 and 9.

Age Distribution of Cases of Paralysis and Aseptic Meningitis

Age in Years	Polio Viruses Isolated		Coxsackie Viruses Isolated		Echo Viruses Isolated	Mumps*	No Viruses Isolated	
	Paralysis	Aseptic Meningitis	Paralysis	Aseptic Meningitis	Aseptic Meningitis	Aseptic Meningitis	Paralysis	Aseptic Meningitis
Virus Diagnosis during 1959								
Under 1	7							2
1–5	30	10		2	1	2	4	11
6–10	9	3		1		2	2	12
11–15	3	3		1	1	1	3	8
Over 15	4	3+3*		1		4		22
Virus Diagnosis during 1960								
Under 1	2		1	2				3
1–5	11			4		1		8
6–10	2	1	1	9		1	2	15
11–15	1	1		2	3	2	1	9
Over 15	1	2	2	12		6		34

* Diagnosed by serology only.

Serological studies identified a further three cases of type 1 poliovirus infection and nine cases of mumps meningitis. Virus diagnosis was therefore made in 38 cases of aseptic meningitis out of 93 (41%).

During 1960.—Stool specimens were received from 24 cases of paralytic disease. Viruses were isolated from 21 (87%). These were six type 1 and 11 type 3 polioviruses, and four Coxsackie group B viruses—two of type 2 and two of type 5. Stool specimens were obtained from 115 cases of aseptic meningitis, and viruses were isolated from 36 (31%). These were one type 1 and three type 3 polioviruses, 29 Coxsackie viruses, and three Echo viruses, all type 9. The Coxsackie serotypes were B5 isolated from 17 cases, B2 from nine cases, B4 from one case, and A9 from two cases. 10 cases were diagnosed serologically as mumps infection. Virus diagnosis was therefore made in 46 cases of aseptic meningitis out of 115 (40%). Stool specimens were received from 11 cases which were clinically either encephalitis or meningo-encephalitis. Coxsackie type B2 was isolated from one, and two others were diagnosed serologically as caused by mumps virus.

Age and Seasonal Distribution.—The Table shows the distribution by age of the patients examined. During both 1959 and 1960 most cases of poliomyelitis confirmed by virus isolation occurred in children 5 years old and under. In contrast, Coxsackie virus infections were more evenly distributed among the various age-groups, and this applied also to those cases in which no virus diagnosis was made. During 1959, when poliovirus type 1 was predominant, virus isolations were made mainly in the summer and autumn months; 29 type 1 viruses were isolated during May and June, 33 during July to October, but it is noteworthy that eight isolations were also made in the winter months. During 1960 almost all the Coxsackie group B and polio type 3 viruses were isolated during August to October. Most of the polio type 1 isolations (five out of seven) were made in the months previous to this period. In both years the cases of mumps meningitis occurred during June to October.

Coxsackie Group B Infections Involving the Central Nervous System

Most of the cases of aseptic meningitis from which Coxsackie viruses were isolated showed no unusual clinical features. There were fever, headache, malaise, anorexia, nausea, sometimes abdominal pains, and occasionally vomiting. After several days these were followed by the features of meningitis. In only 20% of cases, both children and adults, was there a definite two-stage illness, the primary symptoms being followed by a remission of 12 to 48 hours' duration and then by recurrence of fever with symptoms of meningitis. In only 3 out of 39 cases was there a history of muscle pains. One was that of a 38-year-old woman who had generalized aches and pains for three days prior to the onset of meningitis. The other two cases, in patients aged 20 and 43 years, had severe muscle cramps in both legs at the onset of illness. Relapses are common with Coxsackie infections but in the present series this was noted in only one case in which a 16-year-old boy with aseptic meningitis caused by Coxsackie B2 recovered after eight days but relapsed four days later and was ill with meningitis for another three days.

In most cases the cell counts of the cerebrospinal fluid were between 20 and 175, mostly lymphocytes. The extreme abnormal counts were 9 and 490. The protein was normal in half the cases, the others showing small increases, usually to between 60 and 90 mg./100 ml. In three cases with typical features of meningitis the findings in the cerebrospinal fluid were completely normal.

A number of features not usually associated with Coxsackie infection were noted in some cases. Two patients from whom type 5 virus was isolated had a rash. One, a 19-year-old woman, showed a pink macular rash which appeared simultaneously with the onset of the symptoms of meningitis. The other was a 9-year-old boy who gave a history of seven days' headache associated with abdominal pains and a generalized macular rash. All these symptoms cleared up and he was well for 24 hours, after which he developed meningitis and a mild conjunctivitis. Conjunctivitis was noticed to occur simultaneously with the onset of meningeal symptoms in two other patients, both children from whom Coxsackie B2 and B5 viruses were isolated.

Paralysis occurred in four cases, and these are described in some detail.

Case 1.—A 5-year-old boy developed fever, headache, and sudden onset of weakness of the right leg. Examination showed neck stiffness and weakness of the flexor and extensor muscles of the affected limb. The cerebrospinal fluid had a cell count of 40, mostly lymphocytes, and 20 mg. of protein per 100 ml. Coxsackie virus type B5 was isolated from the faeces. Homologous neutralizing antibodies increased from <5 to 500 during the course of the illness. There was no increase in antibodies against polioviruses types 1 to 3. This child had received three doses of polio vaccine. He recovered completely from his illness within seven days.

Case 2.—A 20-year-old-man gave a history of fever, headache, and pains in both arms for about one week. These subsided for about 24 hours and then weakness of the left arm and hand appeared. On admission he had slight fever and definite weakness of the left arm and wrist muscles. Minimal signs of meningeal irritation were present. The cerebrospinal fluid had 160 cells, almost all lymphocytes, and 65 mg. of protein per 100 ml. Coxsackie B5 was isolated from his faeces and the homologous antibodies increased from 5 to more than 500. Polio antibodies showed no increase during the course of the illness. This patient had received two doses of polio vaccine. At discharge four weeks later there was still some slight weakness of the arm.

Case 3.—A 24-year-old woman gave a history of headache and slight sore throat for 10 days. Three days before admission the headache became intensified and pain appeared in the back of the right leg. Twenty-four hours later she could not walk because of weakness of both legs. Shortly before the onset of her illness her husband had headache and sore throat of two days' duration. On examination there was fever, with stiffness of the neck, and a positive Kernig sign. Both lower limbs showed definite weakness of the flexor and extensor muscles, more pronounced on the right side. The cerebrospinal fluid showed a cell count of 112 lymphocytes and 40 mg. of protein per 100 ml. Coxsackie B2 was isolated from the faeces. Sera were not available for antibody studies. She was discharged after three weeks with slight residual weakness of both lower limbs.

Case 4.—A 9-months-old baby with a history of headache and vomiting for one week was found on examination to have fever of 101° F. (38.3° C.) and head-drop due to weakness of the extensor neck muscles. The lumbar fluid was normal. Coxsackie B2 was isolated from the faeces. Sera were not available for examination. Recovery was complete after two weeks.

The one case of severe meningo-encephalitis seen is described because of its unusual course.

Case 5.—A 38-year-old doctor developed fever up to 104° F. (40° C.) and anorexia but without other symptoms and signs. His children had had an obscure minor febrile illness just previously. He recovered after five days. A week later the same symptoms recurred, lasted two days, and then cleared. Three days later fever and headache developed, lasting for three days and followed by severe mental disorientation with complete retrograde amnesia. Examination revealed evidence of meningeal irritation, and the lumbar fluid contained 176 lymphocytes and 180 mg. of protein per 100 ml. The mental changes lasted six days and then ceased almost abruptly, but were succeeded by facial palsy first on one side and then on the other. These resolved over a period of several days, but troublesome paraesthesiae of the upper and lower limbs were noticed during the next eight weeks. Coxsackie virus type B2 was isolated from the faeces. Serum specimens obtained during the initial illness and the early phase of the stage of disorientation showed a rise of antibodies to Coxsackie B2 from <5 to more than 2,000.

An illness in two siblings presented difficulties in clinical diagnosis and was associated with Coxsackie type B4 infection. The infants, 1 and 2 years old, suddenly developed convulsions followed by fever of 102° F. (38.9° C.) and drowsiness. The older child recovered completely in 24 hours, but the other had fever and was listless for three days. The cerebrospinal fluid was normal and so was the blood picture. Bacteriological examinations of the throat, faeces, and urine showed nothing abnormal. Type B4 Coxsackie virus was isolated from the faeces of both children. Serum specimens obtained from the older child showed a significant rise of homologous antibody.

Coxsackie Group B Infections Not Involving the Central Nervous System

During the course of the Coxsackie epidemic a number of unusual syndromes were detected in infants and small children. These included myocarditis and croup.

Case 6.—The most severe case occurred in a 4-month-old boy. He was admitted with a four-days history of fever, anorexia, malaise, and frequent bouts of screaming. When examined his temperature was 102° F. (38.9° C.) and respiration rate 60 a minute. The fauces were injected and he had conjunctivitis. The heart was enlarged and there was a blowing systolic murmur at all areas with a pulse rate of 160 a minute. The liver was enlarged to two finger-breadths below the costal margin. The next day severe stridor was present and also slight neck stiffness. The respiratory distress responded to oxygen and humidity within 24 hours. The child gradually recovered and after 12 days appeared well although the heart remained enlarged. The clinical diagnosis was acute laryngotracheitis and myocarditis. The cerebrospinal fluid, blood, and urine examinations showed nothing abnormal. A throat swab revealed only normal bacterial flora. The Paul–Bunnell test was negative. The electrocardiogram was normal. Coxsackie B5 was isolated from the throat and a rising titre of homologous antibody occurred during the course of illness. Complement-fixation tests showed no evidence of infection with influenza viruses types A, B, and C, parainfluenza viruses types 1, 2, and 3, or adenoviruses.

A further case of myocarditis without laryngotracheitis was seen in a child aged 10 months from whom Coxsackie B5 was isolated. A third child, 4 months old, with B5 infection had severe croup necessitating tracheostomy; there were no other symptoms or signs, and again serological tests for influenza, parainfluenza, and adenovirus infections were negative. The group of cases presenting myocarditis and croup will be described in greater detail elsewhere (Babb, Stoneman, and Stern, 1961).

Coxsackie B5 infections were also noted in association with respiratory infections in older age-groups. Two of these occurred in girls aged 3 and 12 years; the third case was that of a young house-physician attending cases of Coxsackie infection. The symptoms were low fever, coryza, and cough.

Two cases associated with Coxsackie B5 infection were diagnosed clinically as capsulitis or muscle sprain. These were in boys aged 6 and 10 years, with a few days' history of minor febrile illness followed by sudden onset of pain, in the one case in the hip and in the other in the knee. On examination there was marked limitation of movement and tenderness around the joint, but no other symptoms or signs. Complete recovery ensued after 4 and 10 days respectively.

Coxsackie Group A Infections

During 1960 five cases of infection with Coxsackie A9 were noted. Two of these were cases of aseptic meningitis, but the other three were unusual enough to merit comment.

Two of the three cases were in siblings, 1 and 4 years old. They presented simultaneously with headache, followed after 24 hours by persistent vomiting and diarrhoea which lasted for three days. No other abnormalities were found, but Coxsackie A9 was present in the faeces of both.

Parotid swellings, not due to mumps, have been described as occurring in association with herpangina caused by type A Coxsackie viruses (Howlett, Somlo, and Kalz, 1957). The third case in the present group was that of a 6-year-old boy with aseptic meningitis due to Coxsackie A9. Three days after recovery a left-sided parotitis appeared, lasting for 10 days. A throat swab showed normal bacterial flora, and complement-fixation tests were negative for mumps. The serum amylase was only 5 Wolgemuth units.

Discussion

During 1959 poliovirus type 1 accounted for 88% of all virus isolations from cases of disease of the central nervous system, but this dropped to less than 12% the following year, when Coxsackie virus types B2 and B5 became prevalent. Yearly variation in the incidence of enterovirus types is a characteristic of the group. The suppression of the previously dominant virus is probably determined largely by the altered immune status of the population, but perhaps also by interference. There is evidence of such interference between polio and Coxsackie group B viruses. This has been demonstrated not only in animals (Dalldorf, 1951; Stanley, 1952; Sulkin, Wallis, and Murphy, 1953; Dömök, 1957) and in tissue culture (Le Bouvier, 1954; De Lustig and Brieux, 1957) but also in man. Thus epidemiological studies have shown that during epidemics of Coxsackie type B infections paralytic poliomyelitis is uncommon, and vice versa (Dalldorf, 1955; Dalldorf and Albrecht, 1955). On the other hand, a synergistic relationship may exist between polio and Coxsackie group A viruses, and double infections have been reported from some epidemics, possibly being responsible for increased incidence and severity of paralysis (Melnick, Kaplan, Zabin, Contreras, and Larkum, 1951; Dalldorf, 1952).

Poliovirus is the major cause of paralytic poliomyelitis, and the isolation rate of 84% in the present series is similar to that of others in the United States (Lennette, Magoffin, Schmidt, and Hollister, 1959; Brown, Lenz,

and Agate, 1960; Meyer, Johnson, Crawford, Dascomb, and Rogers, 1960) and Denmark (Godtfredsen and von Magnus, 1959). Paralysis is also a common complication of infection with Coxsackie A7 (Chumakov, Voroshilova, Zhevandrova, Mironova, Itzelis, and Robinson, 1956; Ranzenhofer, Dizon, Lipton, and Steigman, 1958; Grist, 1960). It was believed to be very rare after infections with other enteroviruses. However, during the past few years evidence has been accumulating that paralysis may sometimes be associated with other Coxsackie and Echo viruses (Karzon, Barron, Winkelstein, and Cohen, 1956; Kibrick, Meléndez, and Enders, 1957; Buser, Krech, and Moeschlin, 1957; Hammon, Yohn, Ludwig, Pavia, Sather, and McCloskey, 1958; Steigman, 1958; Lennette *et al.*, 1959; Steigman and Lipton, 1960; Johnson, Shuey, and Buescher, 1960; Meyer *et al.*, 1960; Drouhet, 1960). The paralysis is usually slight in degree and transient, but residual palsies may occur.

In the present series four patients, varying in age from 9 months to 24 years, were seen with features indistinguishable from paralytic poliomyelitis. Types B2 and B5 Coxsackie viruses were isolated and serological studies on two of them showed a rising titre of homologous antibody but no evidence of poliovirus infection. As effective vaccination against poliomyelitis becomes more general, so paralytic cases caused by Coxsackie and Echo viruses can be expected to assume an increasingly large proportion of the total (Lennette *et al.*, 1959).

Despite the prevalence of poliovirus type 1 during 1959, only about 24% of cases diagnosed clinically as non-paralytic poliomyelitis and aseptic meningitis were in fact confirmed as poliovirus infections by virus isolation. In this series only a few cases were examined serologically to exclude poliovirus infection, but similar studies by Lennette *et al.* (1959) and Brown *et al.* (1960) showed that virus isolation techniques were about 90% efficient in diagnosing poliovirus infection. In 1959 almost as many cases of aseptic meningitis were caused by Coxsackie and Echo viruses and mumps as by poliovirus. During 1960 the great majority of the virus-confirmed cases of aseptic meningitis were Coxsackie in origin, poliovirus being less commonly isolated. During both years mumps accounted for about 10% of the cases. The virus of lymphocytic choriomeningitis was not encountered at all. An aetiological diagnosis was established in less than half of all cases of aseptic meningitis during the two-year period, which agrees with the findings of other workers (Lennette *et al.*, 1959; Godtfredsen and von Magnus, 1959; McLean, Walker, and McNaughton, 1960). This contrasts with the high rate of diagnosis in cases of paralytic disease. The percentage efficiency of isolating Coxsackie and Echo viruses is not known, and the more extensive use of serological tests for these viruses might well increase the proportion. However, such tests are at present inconvenient for the routine laboratory.

During 1960 most of the isolations of Coxsackie viruses were from cases of aseptic meningitis. It does not follow, however, that this was the commonest clinical syndrome associated with these viruses in the general population, as only the more severe cases would be admitted to hospital. Coxsackie group B viruses cause also mild febrile illnesses often with upper respiratory symptoms and pleurodynia. The latter illness seems to have been relatively uncommon in the present outbreak, perhaps because type 5 seems to be less commonly associated with outbreaks of epidemic pleurodynia than other group B viruses (Dalldorf, Melnick, and Curnen, 1959).

With the usual symptomatology of Coxsackie infection virus isolation and rising antibody titre are usually sufficient to establish a causal relationship, but the situation is very different when an illness with unusual features presents. These viruses cause inapparent infections, and, particularly during periods of epidemic incidence, they may be superimposed on unrelated illnesses. This was exemplified by two cases seen during the present study. One was that of a boy with the typical features of mumps followed by aseptic meningitis. Coxsackie type B5 was isolated from his faeces, and during the course of the illness there was a significant rise of both mumps and Coxsackie B5 antibodies. The second case was that of a man of 45 admitted to hospital with severe diarrhoea. Coxsackie B4 was isolated from his faeces, but later his illness was confirmed as ulcerative colitis. Unusual features can be ascribed to Coxsackie infection only if enough virologically proved cases are seen.

Rash is a rare feature of Coxsackie group B infections (Syverton, 1959; Lycke, Hultgårdh, and Redin, 1959), being more commonly recognized in association with Coxsackie group A and Echo viruses. Two cases of Coxsackie B5 aseptic meningitis in the present series had a transient macular rash.

Two further cases from which Coxsackie viruses were isolated were diagnosed as capsulitis or muscle sprain, and no other cause was found for these illnesses. In view of the tendency of the group B viruses to cause acute localized inflammation of muscles it seems likely that these symptoms were also caused by them. However, pain around joints in association with Coxsackie virus infection has not been previously reported.

Eleven cases of encephalitis or meningo-encephalitis were examined during the 1960 Coxsackie outbreak. Of these, two were due to mumps and one to Coxsackie B2. Coxsackie viruses are recognized as important causes of encephalitis in the United States, where they may be responsible for as many as 15–20% of cases (Lennette *et al.*, 1959). The Coxsackie B2 infection in this series was remarkable for the relapsing course of the febrile illness preceding the meningo-encephalitis. It presented great difficulty to clinical diagnosis, especially in differentiating it from tuberculous meningitis, which is important in view of the rigorous treatment required for the latter. Enteroviruses should be considered especially during the season of their prevalence and if other members of the family have experienced febrile upsets at about the same time or shortly before.

Coxsackie infections in young infants and children may be unusually severe and even fatal. Three infants were seen during the present outbreak with evidence of myocarditis and croup. They are considered in detail in a separate communication (Babb *et al.*, 1961). Indeterminate and brief illnesses also occur in small children. These usually take the form of mild febrile disturbances, occasionally with minor respiratory symptoms, and occur in the summer and autumn months. The four cases described above were more severe and presented difficulty in clinical diagnosis. One pair of siblings had convulsions with high fever and drowsiness, lasting 24 hours and three days respectively. No cause other than Coxsackie B4 in the faeces was found. The other pair, also siblings, had severe vomiting and some diarrhoea, and Coxsackie A9 was isolated from both. The latter cases occurred in the winter months and were clinically

diagnosed as winter vomiting disease. I have noticed similar disturbances of the gastro-intestinal tract in small children undergoing poliovirus infection.

Summary

Virological studies are reported on cases of infections of the central nervous system during a two-year period. Poliovirus type 1 was dominant during 1959, whereas Coxsackie viruses types B2 and B5 were more commonly isolated in 1960.

In 1959 62 paralytic cases occurred. From 53 of these, viruses were isolated, all polioviruses. In contrast, in 1960, from 24 paralytic cases 21 virus isolations were made but only 17 (81%) of these were polioviruses; the rest (19%) were Coxsackie virus types B2 and B5.

In aseptic meningitis, virus diagnosis was made in less than half the patients. In 1959 Coxsackie, Echo, and mumps viruses caused almost as many cases as did poliovirus, and during 1960 Coxsackie viruses were responsible for most. During both years mumps caused about 10% of cases.

Cases of unusual symptomatology associated with Coxsackie infection are described. These include not only paralysis but also meningo-encephalitis and rash. In young children there were cases of myocarditis, croup, and a number of indeterminate but severe illnesses difficult to diagnose clinically.

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REFERENCES

Babb, J. M., Stoneman, M. E. R., and Stern, H. (1961). *Arch. Dis. Childh.* In press.
Brown, G. C., Lenz, W. R., and Agate, G. H. (1960). *J. Amer. med. Ass.*, **172**, 807.
Buser, M., Krech, U., and Moeschlin, S. (1957). *Helv. med. Acta*, **24**, 434.
Chumakov, M. P., Voroshilova, M. K., Zhevandrova, V. I., Mironova, L. L., Itzelis, F. I., and Robinson, I. A. (1956). *Prob. Virol.*, **1**, 16.
Dalldorf, G. (1951). *J. exp. Med.*, **94**, 65.
—— (1952). *J. Mt Sinai Hosp.*, **19**, 396.
—— (1955). *Ann. Rev. Microbiol.*, **9**, 277.
—— and Albrecht, R. (1955). *Proc. nat. Acad. Sci. (Wash.)*, **41**, 978.
—— Melnick, J. L., and Curnen, E. C. (1959). In *Viral and Rickettsial Infections of Man*, 3rd ed., p. 519, edited by T. M. Rivers and F. L. Horsfall, jun. Lippincott, Philadelphia.
De Lustig, E. S., and Brieux, S. (1957). (Abst.). Tissue Culture Ass. Programme of 8th Annual Meeting, Univ. of Maryland School of Medicine, Baltimore, April 16–17, 1957.
Dömök, I. (1957). *Acta microbiol. Acad. Sci. hung.*, **4**, 183.
Drouhet, V. (1960). *Ann. Inst. Pasteur*, **98**, 562.
Godtfredsen, A., and von Magnus, H. (1959). *Dan. med. Bull.*, **6**, 264.
Grist, N. R. (1960). *Lancet*, **1**, 1054.
Hammon, W. McD., Yohn, D. S., Ludwig, E. H., Pavia, R. A., Sather, G. E., and McCloskey, L. W. (1958). *J. Amer. med. Ass.*, **167**, 727.
Howlett, J. G., Somlo, F., and Kalz, F. (1957). *Canad. med. Ass. J.*, **77**, 5.
Johnson, R. T., Shuey, H. E., and Buescher, E. L. (1960). *Amer. J. Hyg.*, **71**, 321.
Karzon, D. T., Barron, A. L., Winkelstein, W., jun., and Cohen, S. (1956). *J. Amer. med. Ass.*, **162**, 1298.
Kibrick, S., Meléndez, L., and Enders, J. F. (1957). *Ann. N.Y. Acad. Sci.*, **67**, 311.
Le Bouvier, G. L. (1954). *Nature (Lond.)*, **174**, 649.
Lennette, E. H., Magoffin, R. L., Schmidt, N. J., and Hollister, A. C., jun. (1959). *J. Amer. med. Ass.*, **171**, 1456.
Lycke, E., Hultgårdh, A., and Redin, B. (1959). *Lancet*, **1**, 1097.
McLean, D. M., Walker, S. J., and McNaughton, G. A. (1960). *Canad. med. Ass. J.*, **82**, 661.
Melnick, J. L., Kaplan, A. S., Zabin, E., Contreras, G., and Larkum, N. W. (1951). *J. exp. Med.*, **94**, 471.
Meyer, H. M., jun., Johnson, R. T., Crawford, I. P., Dascomb, H. E., and Rogers, N. G. (1960). *Amer. J. Med.*, **29**, 334.
Ranzenhofer, E. R., Dizon, F. C., Lipton, M. M., and Steigman, A. J. (1958). *New Engl. J. Med.*, **259**, 182.
Stanley, N. F. (1952). *Proc. Soc. exp. Biol. (N.Y.)*, **81**, 430.
Steigman, A. J. (1958). *J. Mt Sinai Hosp.*, **25**, 391.
—— and Lipton, M. M. (1960). *J. Amer. med. Ass.*, **174**, 178.
Sulkin, S. E., Wallis, C., and Murphy, T. P., jun. (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **84**, 184.
Syverton, J. T. (1959). *Amer. J. trop. Med. Hyg.*, **8**, 101.

PERFORATION OF INTERVENTRICULAR SEPTUM AFTER MYOCARDIAL INFARCTION

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Perforation of the interventricular septum occurring after myocardial infarction is being reported more frequently. In a few cases cardiac catheterization has been used for confirmation and to help in deciding the degree of shunt (Muller *et al.*, 1950; Cooley *et al.*, 1957; Gottsegen *et al.*, 1957; Shickman *et al.*, 1959). In at least three patients the defect has been closed surgically (Cooley *et al.*, 1957; Shickman *et al.*, 1959; Romanoff and Cooley, 1960). After septal perforation, although the patient may survive for a few days, the prognosis is generally poor: Sanders *et al.* (1956), in a collective review of 133 cases, found that 50% died within the first week, and that only 13% lived for more than two months. In occasional instances a patient has lived for some years afterwards (Wood and Livezey, 1942; Zucker *et al.*, 1952; Briggs and Holt, 1954). The longest recorded survival time was that of a patient of Schlappi and Landale's (1954), whose acquired ventricular septal defect occurred in 1947, she eventually died from a non-cardiac condition at the age of 83 (Schlappi, 1960, personal communication).

Historical Note

Dr. P. Mere Latham (1846) gave a detailed account of the terminal illness of a patient who can now be diagnosed from the history as having suffered an attack of myocardial infarction. On the fifth day (Friday) after the onset of his patient's cardiac pain there was a recurrence of a more severe attack of pain, and Dr. Latham wrote:

"But on the next day, Friday, I was suddenly called to him. It was six p.m. I found that, about an hour before, the pain had returned with far greater severity than ever. He was deadly pale, and from the centre to the extremities of his body he was cold as marble, and streaming with perspiration; but his pulse was of a good strength, and his heart was contracting regularly and forcibly, and now, for the first time (according to my observation), with a loud systolic murmur, audible in the precordial region, and not in the arteries. I administered a large dose of opium with ether and ammonia. Visiting him again in an hour or two, I

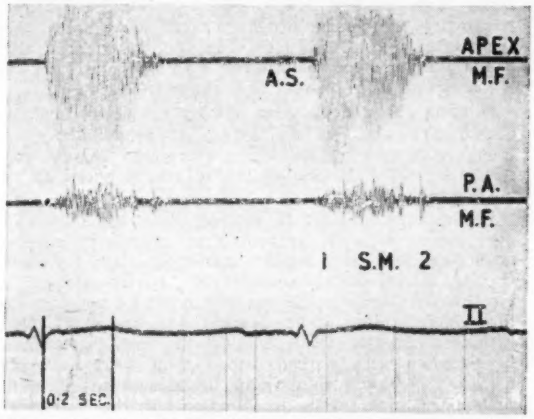

FIG. 1.—Case 1. Phonocardiogram showing (upper record) loud pansystolic murmur at the apex with small atrial sound and (lower record taken over pulmonary area) transmitted systolic murmur with pulmonary second sound. A.S.=Atrial sound, S.M.=Systolic murmur. M.F.=Medium frequency. P.A.=Pulmonary artery.

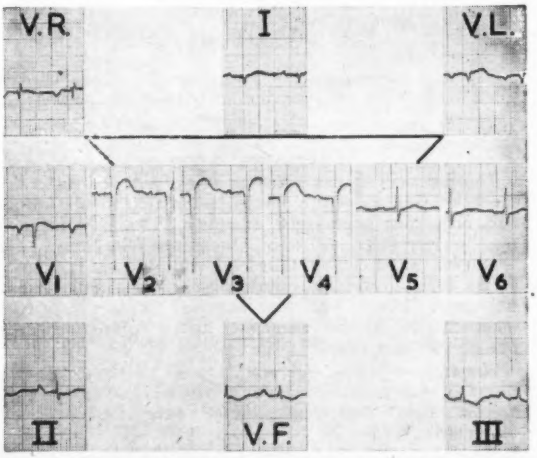

FIG. 2.—Electrocardiogram showing antero-septal myocardial infarction with suggestion in leads V_2–V_4 of ventricular aneurysm.

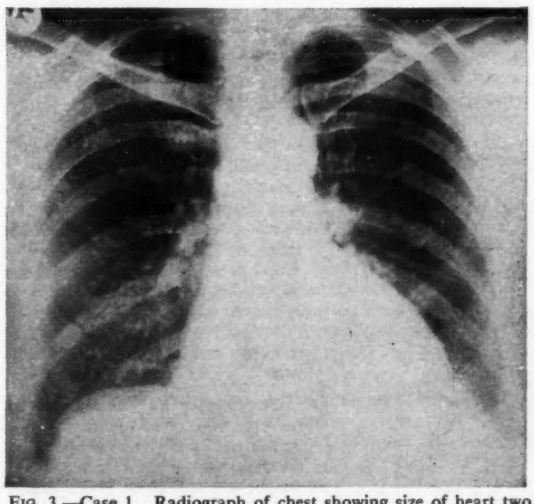

FIG. 3.—Case 1. Radiograph of chest showing size of heart two years prior to admission.

found the pain unabated, and his pulse beginning to sink. I staid with him through the night, still giving at intervals opium and ether and ammonia, and applying external warmth, but all to no purpose. Still the pain did not lessen. Still he looked and he felt like a corpse, he was so pale and so cold. At four in the morning (Saturday) the pulse finally ceased to be felt in the arteries, while yet the heart was perceived by the ear to move, but not by the hand. In this state he survived seven hours longer, until, with his mind clear to the last, he died at 11 a.m. Let me add, what I shall not soon forget, that this good man endured eighteen hours of mortal agony with wonderful patience and resignation.

"Upon examination after death, all the interior structures of the body were found more loaded with fat than its external appearance would have led me to expect. We looked only superficially to the abdomen, where we found nothing remarkable but a vast accumulation of fat within the mesentery. Our attention was chiefly directed to the suspected seat of disease—the chest. Here the lungs were perfectly healthy. The heart was a good deal larger than natural as a whole and incased in fat. It was upon its right side that the fat was accumulated to the greatest amount, and its muscular substance was everywhere very flaccid and very thin, and became thinner and thinner as you approached the apex when it was reduced to a mere line. Yet, thin as it was, it was quite healthy in colour and preserved all the visible characters of muscle without any intermixture of fat. The fat was all exterior to it. The capacity of the right ventricle was notably larger than natural. Its internal lining was stained of a deep red. Its orifices were free, and its valves healthy. On its left side it was less covered with fat. Here the ventricle was considerably dilated. The muscular substance was considerably hypertrophied. It preserved its healthy character, both of colour and consistence in the external parietes: but in the septum it was pale and soft, manifestly in consequence of fatty degeneration. In the septum, at its posterior juncture with the parietes, there was an oblique rent passing through it from ventricle to ventricle. On the side of the left ventricle it was an inch and a half in length; on the side of the right it just opened at a point. In truth, while we were examining the right side, the rupture passed undiscovered. The orifices of the left, as of the right ventricle, were quite free, and its valves healthy. The coronary arteries contained some atheromatous deposits, but were quite pervious. The aorta was healthy as far as its arch. It began to be studded with atheromatous and earthy matter in its descending portion."

The purpose of reporting three further patients, one of whom survived for three years after a septal perforation, is to emphasize the auscultatory and haemodynamic findings in this condition. There was necropsy confirmation in each case.

Case 1

A 64-year-old housewife had experienced sharp pains under the sternum for two weeks; three days before admission these became more severe and radiated to the left side of the chest, then during the next 48 hours she had frequent attacks of acute dyspnoea, each of which lasted for about five minutes. Her husband observed that during these attacks her heart seemed to gallop; he had also felt a thrill in the centre of his wife's chest, which he described as "like the purring of a cat." When her own practitioner visited her she was in a moribund state and was admitted immediately to St. James' Hospital (May 12, 1957).

On examination she was shocked, cold, and sweating; temperature 96° F. (35.6° C.); pulse was of poor volume, 80 a minute, regular rhythm. The respirations were 20 a minute and the blood-pressure 145/80. There was a harsh, coarse systolic thrill and murmur situated between the left sternal edge and the apex; the murmur was conducted to the left axilla. An electrocardiogram showed an anterior myocardial infarction (Fig. 2). E.S.R. was 65 mm. in the first hour; the white blood count was 26,000/c.mm.

Congestive cardiac failure developed with orthopnoea, raised jugular venous pressure, and peripheral oedema. She was treated with digitalis and mersalyl; and *x*-ray examination of her chest, taken on May 16, showed her heart was enlarged to the left and right, compared with a routine chest film taken in 1955 (Fig. 3), when she was on the staff of another hospital. She remained critically ill and on May 25 had an attack of rapid auricular fibrillation lasting some hours. During these weeks she was easily exhausted, and it was not until June 5 that she was able to sit out for bed-making. At this time the jugular venous pressure became raised with marked "A" and "V" waves, and the pulmonary component of the second heart sound was accentuated (Fig. 4): an E.C.G. on June 7 showed healing of the anterior myocardial infarct, with right axis deviation. A radiograph taken on June 18 is shown in Fig. 5.

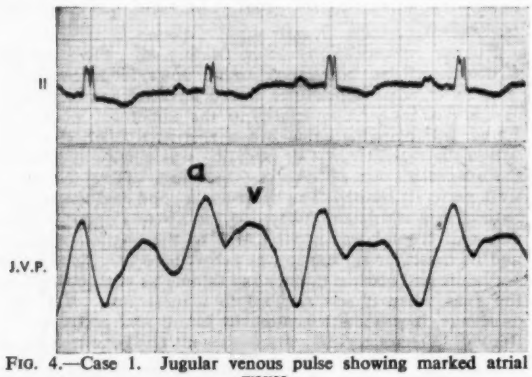

FIG. 4.—Case 1. Jugular venous pulse showing marked atrial waves.

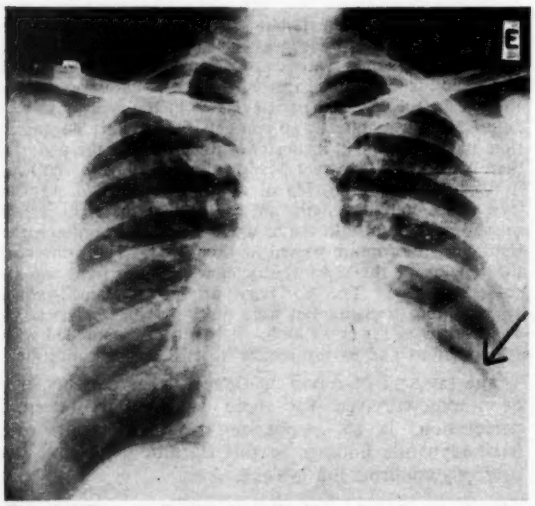

FIG. 5.—Case 1 Radiograph of chest taken five weeks after admission showing ventricular aneurysmal bulge marked by arrow.

In early July the question whether the defect might be closed surgically was discussed. As septal perforation usually occurs only when there is widespread atherosclerosis of the coronary arteries, a decision against operation was made on this account.

By September the E.C.G. showed persistent ST elevation over the septal leads, suggesting an antero-septal cardiac aneurysm with first-degree heart-block, and screening revealed a small cardiac aneurysm at the left lateral cardiac border. By December she was able to live a quiet, restricted life. A recurrence of her oedema was treated effectively with chlorothiazide. By July, 1958, the signs of pulmonary hypertension were marked with a giant "A" wave plus 6 cm. There was splitting of the second sound in the pulmonary area, with accentuation of the pulmonary component; a persistent cough with mucopurulent sputum occurred.

She was able to go out for walks, needing maintenance therapy of digitalis and chlorothiazide. She attended as an out-patient periodically, and during the next 18 months the E.C.G.s showed no change. In November, 1959, there was a recurrence of congestive heart failure, with tricuspid incompetence, which responded to increased doses of chlorothiazide.

She died suddenly at home on June 30, 1960, just over three years from the time the ventricular perforation had occurred.

Post-mortem Findings

The pericardium was adherent to the anterior surface of the heart (Fig. 6), where a very large patch of old fibrosis had undergone aneurysmal dilatation. The right ventricle was hypertrophied to twice its normal thickness. The aneurysm was actually found to constitute a ventricular septal defect; the left ventricle was also slightly hypertrophied. There was no valvular disease; advanced atheromatous changes were seen in the coronary arteries, but no clot was found.

Respiratory System.—A pint (584 ml.) of free fluid was found in each pleural cavity, and there were some adhesions at the right base: both lungs were congested and oedematous.

Intestinal System.—Cardiac cirrhosis and nutmeg changes were seen in the liver; there were several pints of free fluid in the abdominal cavity. The kidneys were finely granular. The spleen was congested and firm. The endocrines were normal.

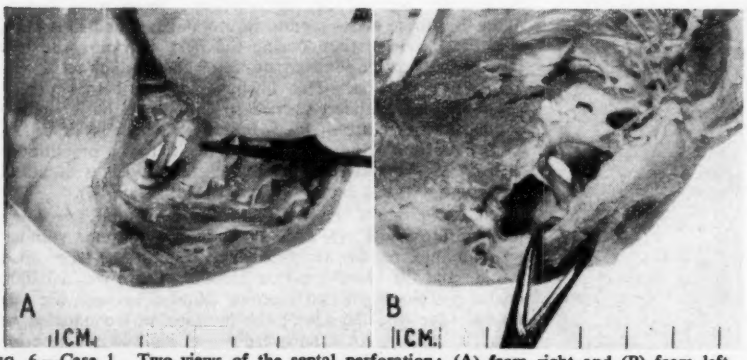

FIG. 6.—Case 1. Two views of the septal perforation: (A) from right and (B) from left ventricle showing aneurysm in the left ventricle with adherent pericardium. Note bar of intact myocardium across perforation marked by arrow.

Case 2

A 75-year-old retired man was admitted to St. James' Hospital on February 25, 1960, with a left hemiplegia, which had occurred three days previously. There was no past history of chest pain or winter cough. A diagnosis of cerebral thrombosis was made. On examination the heart sounds were normal, no thrill or murmurs were present; blood-pressure 245/140 mm. Hg; pulse 72 a minute, regular rhythm. With physiotherapy he made slow but steady progress, and after two months was walking fairly well with a stick.

On May 9 he complained for the first time of severe central, low substernal pain, which he later described as a dull ache, like a weight on his chest. On examination the heart sounds were normal, there were no murmurs

or thrill; blood-pressure 190/115 mm. Hg; pulse 48 a minute, regular rhythm. An electrocardiogram showed a recent posterior myocardial infarction (Fig. 7), with a Q–S complex in AVF, and lead III with raised, coved ST segments and biphasic T waves.

He was treated by bed rest, and 50 mg. of pethidine gave relief; he had no more severe pain. On May 26, at 3.15 a.m. he wakened suddenly, intensely dyspnoeic, complaining of abdominal pain; he was cyanosed; blood-pressure 140/110, pulse 136 a minute and regular. There was now a loud, coarse systolic thrill and murmur at the lower left sternal edge (Fig. 8). He was given pethidine, aminophyllin, digitalis, and mersalyl. After a few hours the dyspnoea had improved, and it was seen that the jugular venous pressure was raised to the angle of the jaw, with marked "A" waves. An electrocardiogram on May 26 showed a tachycardia of 116 a minute with healing of a posterior infarction. Treatment with digitalis and mersalyl was continued. His jugular venous pressure fell to normal, blood-pressure 100/70 mm. Hg, pulse 72 a minute, regular rhythm. No peripheral oedema; he continued fairly well until July 31, when at 6.45 a.m. he suddenly collapsed and died, 83 days after his myocardial infarction and 66 days after the perforation of his ventricular septum.

Post-mortem Findings

Cardiovascular System.—The heart weighed 420 g.; the pericardium was adherent over a small area posteriorly: there was atherosclerotic thickening of the mitral and aortic valves; the posterior wall of the interventricular septum had an ovoid perforation 1.5 by 1 cm., surrounded by a ring of dense fibrosis (Fig. 9). The coronary vessels were narrowed by calcific atherosclerosis. The aorta showed calcific atherosclerosis with much ulceration and thrombosis of the left common iliac artery: the main vessels showed a similar picture.

Respiratory System.—Both pleural cavities were full of pale green fluid; the lungs were oedematous and showed basal congestion.

Alimentary System.—A constriction was found in mid-stomach due to scarring from previous ulceration.

The liver showed early nutmeg change. The endocrines and the spleen were normal.

Genito-urinary System.—Severe bilateral nephrosclerosis with cortical cysts and reduction of the cortices; the capsule stripped, leaving a granular surface; the bladder was dilated and the prostate enlarged.

Central Nervous System.—Two small cysts were found in the right cerebral hemisphere.

Case 3

A 66-year-old housewife was first admitted to St. James' Hospital in March, 1960 in hypoglycaemia. She rapidly recovered after the administration of glucose, and then gave a history of diabetes mellitus, treated by diet and insulin, for the previous 16 years: during this period she had been admitted to various hospitals on about four occasions for hypoglycaemic attacks.

On examination there was no diabetic retinopathy. Cardiovascular system: heart sounds were normal, with a short aortic ejection systolic murmur; rhythm regular. The pedal pulses were not felt. The central nervous system showed no evidence of peripheral neuropathy.

Investigations.—Urine: a faint trace of albumin. Chest radiography, normal. Blood count, normal. Serum cholesterol and liver-function tests within normal limits: fasting blood sugar, 179 mg./100 ml.

Her diet and insulin were adjusted and she was discharged home on May 4. She remained well until she was again admitted as an emergency case on September 29, with a history of precordial pain, radiating to her neck, for one week prior to admission.

On examination she was acutely ill: the jugular venous pressure was not raised; the pulse was of poor volume, regular rhythm, rate 100 a minute; blood-pressure, 120/85 mm. Hg. On auscultation there was a triple rhythm at the apex and a pericordial friction rub audible over an area to the left border of the sternum in the fourth intercostal space; there was ankle oedema. An electrocardiogram

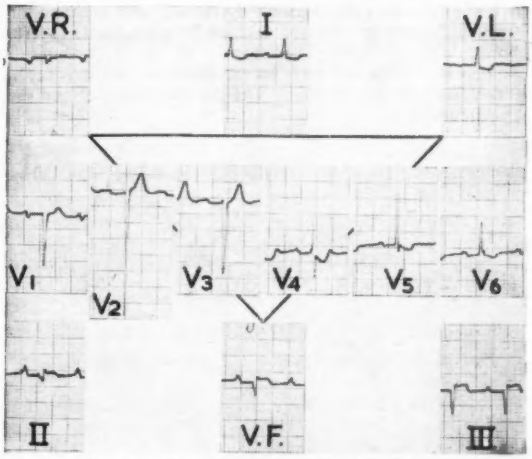

FIG. 7.—Case 2. Electrocardiogram showing posterior cardiac infarction.

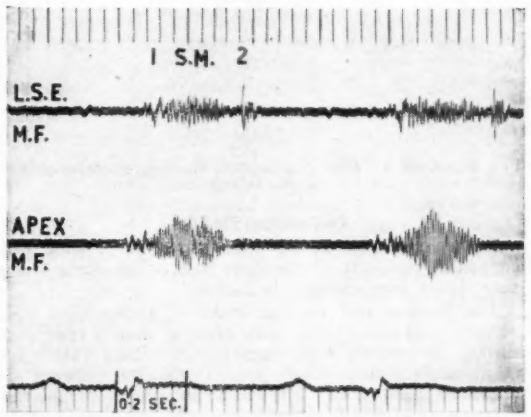

FIG. 8.—Case 2. Phonocardiogram. Lower record: medium frequency at apex showing pansystolic murmur. Upper record: medium frequency left sternal edge fourth interspace. S.M.= Systolic murmur. L.S.E.=Left sternal edge. M.F.=Medium frequency.

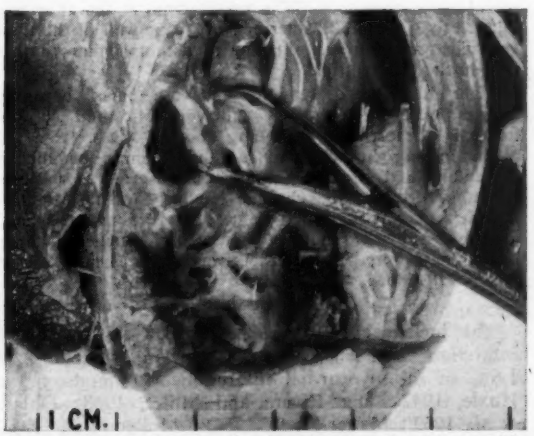

FIG. 9.—Case 2. Septal perforation view from the right ventricle.

showed a recent extensive anterior myocardial infarction with right bundle-branch block (Fig. 10). Soluble insulin was given for her diabetes, the pulse remained rapid and weak; the area over which a pericardial friction rub was audible increased in size. On October 3 her blood-pressure fell to 110/80 mm. Hg and a left hemiparesis developed; a few hours later she became dyspnoeic, and a pansystolic thrill and murmur occurred midway between the left sternal border and the apex. Perforation of the interventricular septum was diagnosed after an extensive anterior myocardial infarction with pericarditis. The patient collapsed and died two hours later.

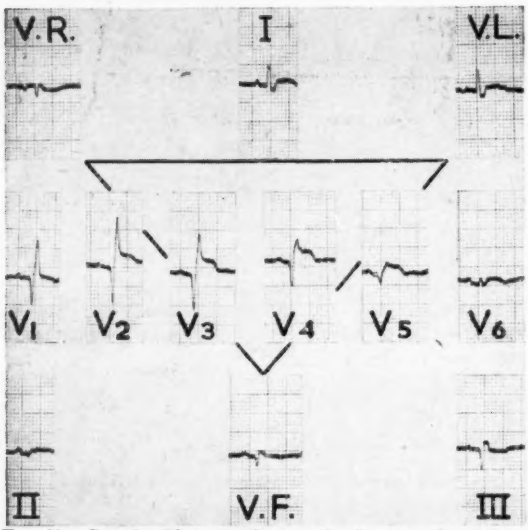

FIG. 10.—Case 3. Electrocardiogram showing extensive antero-septal infarct.

Post-mortem Findings

At necropsy (Dr. P. W. Kippax) the lungs were very congested, especially at the right base, where there was a very recent haemorrhagic infarction.

The parietal and visceral layers of pericardium were adherent and separated in some areas to show a roughened surface, in others a shaggy appearance. There were a few small pockets of yellowish necrotic material between the adherent membranes. The distal two-thirds of the left ventricle showed full-circumference infarction, some of it partially healed, but with evidence of recent haemorrhagic infarction and areas of liquefaction necrosis. The infarction had produced an interventricular septal defect towards the apical end of the septum, which was partially closed by recent mural thrombus. The myocardium at the apex was thinned to 3 mm. The anterior part of the wall of the right ventricle was infarcted, showing a picture similar to that seen in the left ventricle.

Right anterior descending and circumflex coronary arteries were all extremely atherosclerotic and showed internal haemorrhages beginning about 1.5 cm. from the ostium in the right and 1 cm. from the ostium in the anterior descending and circumflex branches. There was a mural thrombus deep to the chordae tendineae of the anterior mitral cusp, but no septal defect was demonstrated here. The liver showed a nutmeg pattern and weighed 1,480 g. The kidneys were pale and there was a small healed infarct in the left kidney.

Discussion

The incidence of septal perforation in myocardial infarction has been reported as varying from 0.9% to 1.6% of all myocardial infarctions (Edmondson and Hoxie, 1942; Diaz-Rivera and Miller, 1948; Oblath *et al.*, 1952; Maher *et al.*, 1956). Muller *et al.* (1950) stressed the difficulty in finding such perforations even when the pathologists were searching for this condition.

The clinical history is usually characterized by the cardiac pain due to the myocardial infarction, followed after a period of 3 to 16 days by a sudden change in the condition of the patient; this may present as acute pulmonary oedema, tachycardia, raised venous pressure with prominent "A" wave, enlargement of the right side of the heart, and production of loud systolic murmur, often with a thrill, maximal between the left sternal edge and the apex in the fourth and fifth left intercostal spaces. The murmur may simulate that of organic mitral incompetence in that it is pansystolic and may include the aortic element of the second sound and radiates into the axilla. This differs from the murmur of congenital septal ventricular defect, in which the murmur is usually localized to the lower left sternal edge. This difference may be due in part to the different anatomical situation of the defect and in part to the different haemodynamic situation in acute and chronic forms.

Confusion may arise between the murmur of functional mitral incompetence due to dilatation of the left ventricle, but a loud murmur with thrill appearing during the course of the recovery phase of myocardial infarction should make one consider the diagnosis of perforation of the septum. Pericardial rub and ruptured papillary muscle must also be considered in the differential diagnosis. The effect on the circulation is to produce an acute left-to-right shunt with an increase in pulmonary blood-flow and load on the right heart. The venous pressure rises with a prominent "A" wave, and the sudden increase in pulmonary flow may result in pulmonary oedema. During the course of time increasing pulmonary hypertension may occur. Although cardiac catheterization has been used to confirm an acquired septal defect in cases of traumatic septal rupture, this procedure carries a very definite risk in a patient with a recent myocardial infarct. Muller *et al.* (1950) performed cardiac catheterization in a patient six months after myocardial infarction with septal perforation: they found increased pressures in the right ventricle and pulmonary artery with an oxygen content higher than that in the right atrium; the calculated left-to-right shunt was 5.2 litres a minute. Other workers have confirmed these findings (Cooley *et al.*, 1957; Gottsegen *et al.*, 1957). The use of dye-dilution curves in our first two cases confirmed the diagnosis by showing the presence of a left-to-right shunt (Swan and Wood, 1957; Oakley *et al.*, 1960).

Pathology.—Rupture of the interventricular septum usually accompanies widespread coronary arterial disease. The immediate cause of rupture is occlusion of either the left anterior descending coronary artery or its branches, or the right coronary artery. In the former the rupture tends to be towards the anterior part of the septum, and in the latter more posteriorly. The rupture is often difficult to see and may be missed on routine post-mortem examination, especially when hidden by blood clot or covered by papillary muscles. In Case 1 a strand of intact papillary muscle actually crossed the septal perforation. It is difficult to assess the speed with which fibrosis develops after the incident, as there are usually widespread atherosclerotic changes, and fibrotic areas may well have been formed at an earlier stage. The blood supply to the area was poor in our cases, and one can only speculate on what the result of inserting sutures through this area would be.

Prognosis.—Our first patient is of interest because of the long survival period. A significant feature of septal perforation is that death does not occur immediately: Edmondson and Hoxie (1942) found an average period of survival of 7.4 days. In the series of Sanders *et al.* (1956) 13% (12 patients) lived from two months to several years.

Treatment.—The general principles of treatment are based on the knowledge that the efficiency of the heart in which septal perforation has occurred has already been impaired by coronary atherosclerosis followed by myocardial infarction. The left-to-right shunt, with increased blood-flow and raised pressure in the pulmonary circulation, throws an extra strain on the ventricles, and leads to heart failure. In our first two cases the administration of digitalis was of benefit, and diuretics were of considerable help. In Case 1, after a few weeks, there was a loss of response to mercurial diuretics: chlorothiazide with potassium supplements had an immediate beneficial effect.

Summary

Three cases of ventricular septal perforation are described. The diagnosis should be considered when a patient with an acute myocardial infarction suddenly deteriorates and develops a loud blowing pansystolic murmur between the left sternal edge and apex in the fourth and fifth left intercostal spaces. Dye-dilution curves in two cases showed the presence of a left-to-right shunt.

We thank Professor J. McMichael for his advice and encouragement, Dr. D. Emslie-Smith for the phonocardiograms, and Miss E. Mason for the photographs.

References

Briggs, J. F., and Holt, J. (1954). *Amer. Heart J.*, **47**, 926.
Cooley, D. A., Belmonte, B. A., Zeis, L. B., and Schnur, S. (1957). *Surgery*, **41**, 930.
Diaz-Rivera, R. S., and Miller, A. J. (1948). *Amer. Heart J.*, **35**, 126.
Edmondson, H. A., and Hoxie, H. J. (1942). Ibid., **24**, 719.
Gottsegen, G., Szám, I., Romoda, T., and Matheides, P. (1957). *Acta med. scand.*, **158**, 157.
Latham, P. M. (1846). *Lectures on Clinical Medicine, Comprising Diseases of the Heart*, 2nd ed., **2**, 168. Longman, London.
Maher, J. F., Mallory, G. K., and Laurenzi, G. A. (1956). *New Engl. J. Med.*, **255**, 1.
Muller, O., Humerfelt, S., Rasmussen, H., and Storstein, O. (1950). *Acta cardiol. (Brux.)*, **5**, 633.
Oakley, C., Taylor, S., Wilcken, D., Hollman, A., Goodwin, J. F., and Shillingford, J. (1960). *Brit. Heart J.*, **22**, 533.
Oblath, R. W., Levinson, D. C., and Griffith, G. C. (1952). *J. Amer. med. Ass.*, **149**, 1276.
Romanoff, H., and Cooley, D. A. (1960). *Israel med. J.*, **19**, 103.
Sanders, R. J., Kern, W. H., and Blount, S. G. (1956). *Amer. Heart J.*, **51**, 736.
Schlappi, J. C., and Landale, D. G. (1954). Ibid., **47**, 432.
Shickman, M. D., Fields, J., Pearce, M. L. (1959). *Arch. int. Med.*, **103**, 140.
Swan, H. J. C., and Wood, E. H. (1957). *Proc. Mayo Clin.*, **32**, 486.
Wood, F. C., and Livezey, M. M. (1942). *Amer. Heart J.*, **24**, 807.
Zucker, R., Leibowitz, S., Brody, H., and Sussman, R. M. (1952). *Arch. intern. Med.*, **89**, 899.

About one child in every 600 born in this country is a mongol, and the National Association for Mental Health has published a booklet, *A Letter to Parents of a Mongol Baby*, prepared by a children's specialist, which will be of help to those concerned with what, how, and when to tell the parents that their child suffers from this condition. (N.A.M.H., 39 Queen Anne Street, London W.1, price 1s. 3d.)

EXPERIMENTAL AND CLINICAL OBSERVATIONS ON POLDINE IN TREATMENT OF DUODENAL ULCER

BY

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The gastric secretion of acid by a patient with duodenal ulcer in response to a glucose test meal is about halved if an effective dose of poldine methosulphate (" nacton ") is taken beforehand (Douthwaite and Hunt, 1958). The drug also reduces gastric secretion of acid in response to a large dose of histamine (R. Seidelin, 1960, personal communication). These observations, made under strictly controlled experimental conditions, suggest that the drug might be useful in the treatment of duodenal ulcer. To investigate this possibility, the effect of the drug on the acidity of gastric contents has been investigated under the conditions of clinical use, and the drug has been subjected to a small controlled therapeutic trial.

Experimental Observations

Observations are reported on 16 patients with an uncomplicated radiologically proved duodenal ulcer. All were admitted to hospital, they were allowed up, and drugs other than poldine and sedatives were withheld unless stated otherwise. The individual dose of poldine for each patient was found by giving increasing doses until side-effects appeared. The initial dose given was 7.5 mg. daily, divided into three doses, or 12.5 mg., divided into five doses, and the total dose was increased by 7.5 or 12.5 mg. each day. If the first side-effects to appear were trivial the dose was further increased until definite side-effects developed. The dose just below that producing uncomfortable side-effects was defined as the " optimum " dose.

On the days of the test, samples of gastric contents were withdrawn every hour, on the hour, for 24 hours through a fine naso-gastric tube placed radiologically so that the aspiration holes lay in the likely position of the gastric antrum. The *p*H of the samples was measured with a sealed glass electrode. Doses of the drug, food, and drinks were given immediately after a sample was withdrawn.

Gastric Acidity of Patients Taking Gastric-type Diet

The effect of different doses of poldine was studied under these conditions in 16 patients. Observations made on a control day without poldine were compared with observations made on days when the drug was given. The control observations were made first in 13 patients and last in three patients. Four patients were studied while the dose of poldine was being increased and at a time when they were experiencing no side-effects from the drug; two patients were studied on one day at daily doses of 30 and 40 mg. respectively, the other two patients were studied on two days at daily doses of 30 and 60 mg., 30 and 90 mg., respectively. Of 10 patients taking the drug in the optimum dose, nine received five daily doses and the other patient three daily doses. Four of these patients had received the drug continuously in the optimum dose for periods of 1, 4, 9, and 12 days respectively before the test. The results in these four

patients did not differ from those in patients who began the optimum dose (found by previous trial) on the day of the test. Three patients were studied at a time when they were experiencing severe side-effects from the drug. The results from all the patients are combined in Figs. 1 and 2. Each section of the histogram in Fig. 1 shows the total number of samples in a particular *p*H range on the control day and on the day when the drug was given. Fig. 2 shows the mean acidity on an arithmetic scale at each hour of the day. It is clear that in patients taking a ward gastric-type diet, poldine did not affect the acidity of the gastric contents whether given in a dose insufficient to produce side-effects, in the optimum dose, or in a dose producing side-effects too severe to be tolerated as a maintenance treatment.

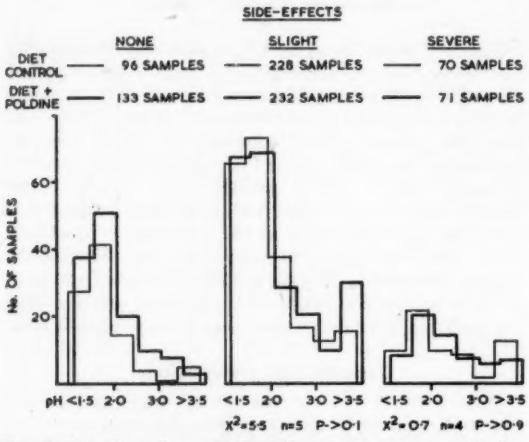

FIG. 1.—Number of samples in different *p*H ranges on the day when poldine was given compared to the control day. No difference between the two days is apparent even when poldine was given in a dose large enough to produce severe side-effects. Differences between the distribution of the samples have been assessed by the χ^2 test except in the series with no side-effects, where two observations at different doses of poldine were made in two of the four patients (n=5, unless the number of samples in any range was small, when two adjacent ranges were combined).

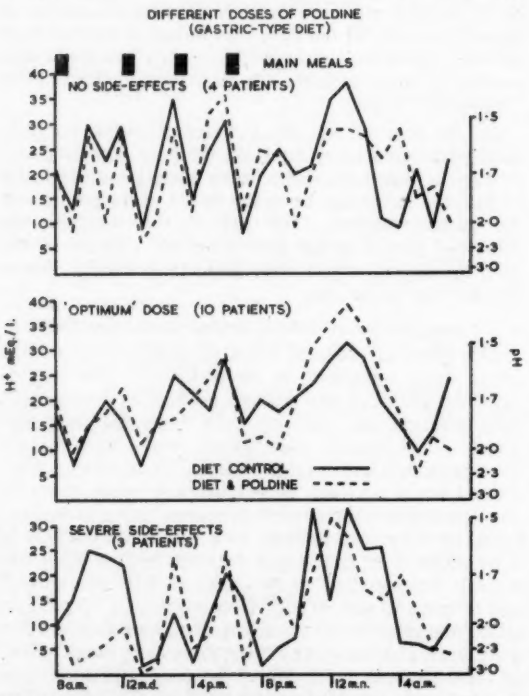

FIG. 2.—Mean acidity at each hour of the day on the day when poldine was given compared with the control day.

Gastric Acidity Under Special Dietary Conditions

Some other antisecretory drugs have been shown to lower gastric acidity, as measured by the sampling technique, when patients take hourly drinks of a milk–cream mixture without other food. The effect of poldine under these conditions has been compared with the effect when the same patients took a standard diet. Four patients were each studied during four 24-hour periods: hourly milk–cream drinks, with and without poldine; and on the diet, with and without poldine. The order of these 24-hour periods was varied from patient to patient in a latin-square pattern. Details of the method employed and the standard diet used are described elsewhere (Bingle and Lennard-Jones, 1960). Poldine was given in the optimum dose, five times daily. The

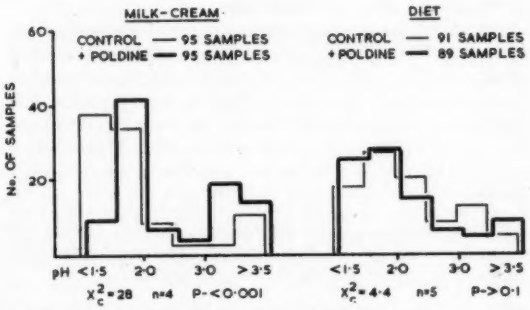

FIG. 3.—Distribution of samples in different *p*H ranges when patients took poldine in the "optimum" dose with hourly milk–cream drinks and with a standard bland diet. There was a significant ($P<0.001$) reduction in the proportion of samples *p*H<1.5 when patients took poldine with milk–cream drinks.

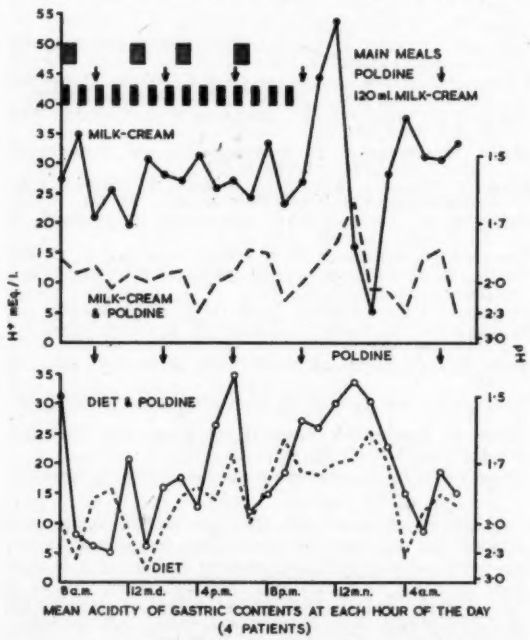

FIG. 4.—Mean acidity at each hour of the day when poldine was given with milk–cream drinks and with diet.

results, depicted in Figs. 3 and 4, show that there was a significant ($P<0.001$) reduction in the number of very acid samples, below *p*H 1.5, when milk–cream drinks were taken with poldine and a corresponding reduction in the mean acidity throughout the day. There was no suggestion of reduced acidity when the same patients took the diet.

Observations on Gastric Emptying at Night

By giving two charcoal tablets at 10 p.m. and observing the presence or absence of charcoal in subsequent samples it is possible to gain some information about gastric emptying. The accuracy of the method is limited by the apparent tendency of the charcoal to sediment, so that it may not appear in samples early during the night, and by the difficulty of determining the end-point. In this study the end-point has been taken as the last sample containing much charcoal, although traces of charcoal may appear in several subsequent samples. The results of 15 observations in eight patients are shown in Fig. 5. It will be seen that charcoal generally persisted longer when poldine was taken in the optimum dose. The mean time was 3.4 hours on the control day and 6.1 hours when the drug was taken; the difference of 2.7 hours is significant ($P<0.001$).

Gastric Acidity in Patients Taking a Standard Diet and Alkali

A drug which reduces gastric secretion, gastric motility, or both is likely to increase the effectiveness of alkali given by mouth. This has been investigated in three patients by giving them repeated small doses of alkali—enough to reduce gastric acidity a little—and then adding poldine to see if acidity was reduced further. The dose of tab. mag. trisil. co., sucked between meals from 7 a.m. to 9 p.m., which was just sufficient slightly to reduce gastric acidity, was found for each patient by preliminary experiment. After control observations had been made, the effect of adding poldine to this regime in optimum dose, five times daily, was studied. The same patients were also given a large dose of alkali at 10 p.m. to see if poldine prolonged its effect. The results are shown in Figs. 6, 7, and 8.

During the day, between 7 a.m. and 9 p.m., poldine apparently augmented the effect of the alkali, but there is nothing to suggest that poldine prolonged the effect of the dose of alkali given at bedtime.

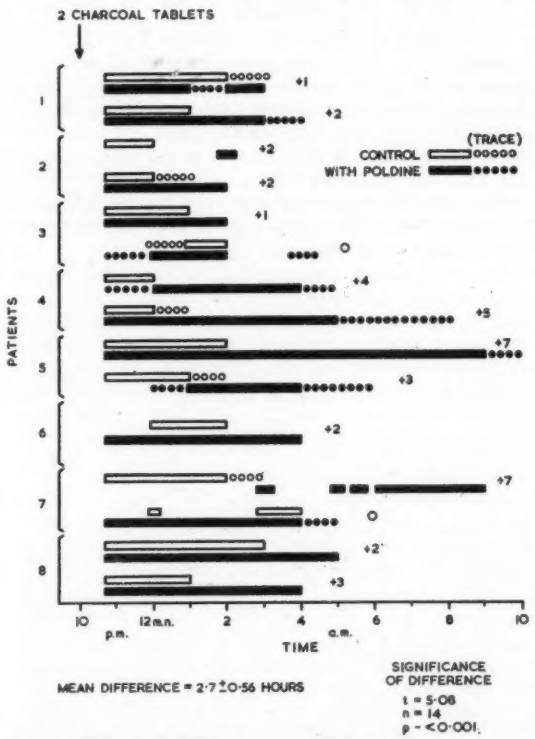

FIG. 5.—Diagram showing times at which charcoal was present in nocturnal samples after two charcoal tablets had been given at 10 p.m. 15 observations in eight patients. Charcoal persisted significantly ($P<0.001$) longer when poldine was given in optimum dose than when poldine was not given.

A Controlled Therapeutic Trial

To be clinically useful a new remedy for duodenal ulcer should succeed where simpler measures have failed. For this reason the patients selected for this trial were those in whom simple measures had either failed to control the pain from the ulcer or had failed to prevent frequent exacerbations of pain.

Design of the Trial

A double-blind trial was planned but proved unworkable in practice, since the active tablet gave rise to marked side-effects but the placebo did not. Patients

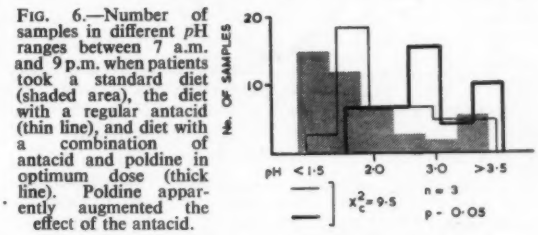

FIG. 6.—Number of samples in different *p*H ranges between 7 a.m. and 9 p.m. when patients took a standard diet (shaded area), the diet with a regular antacid (thin line), and diet with a combination of antacid and poldine in optimum dose (thick line). Poldine apparently augmented the effect of the antacid.

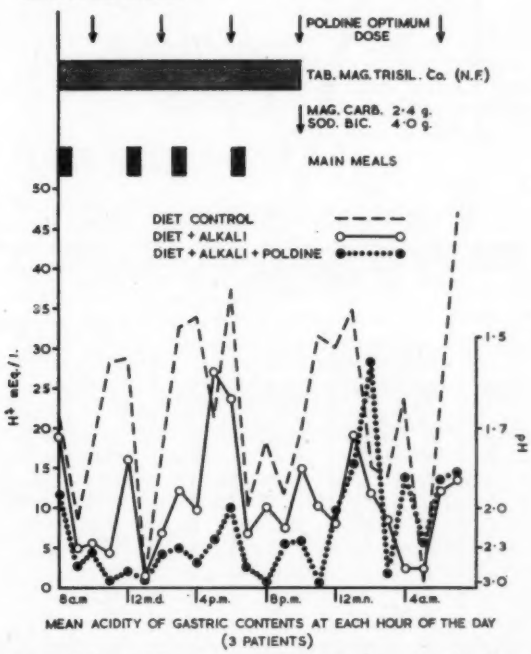

FIG. 7.—Mean acidity at each hour of the day with diet alone, diet and antacid, and diet with a combination of antacid and poldine in optimum dose.

in whom a recent barium-meal examination showed a duodenal-ulcer crater without delayed gastric emptying, and who were regarded as suitable because simple treatment had failed, were invited to enter a trial of two new remedies for their ulcer. Details about the 11 patients who completed the trial are set out in Table I. The two drugs used were poldine and an identical control tablet. The patients were given much personal attention and advised about alteration of their mode of life if this seemed necessary. In addition to the treatment under trial, alkalis were given to control pain, and sedatives were given if indicated. The trial lasted six months, and each trial tablet was given for three months, so that every patient who completed the trial acted as his own control; the order in which the treatments were given was randomized. The patients were warned that the trial would initially involve weekly visits to the clinic while the correct dose of the drug was being found and that the trial involved treatment for three months with the correct dose of each of the two drugs.

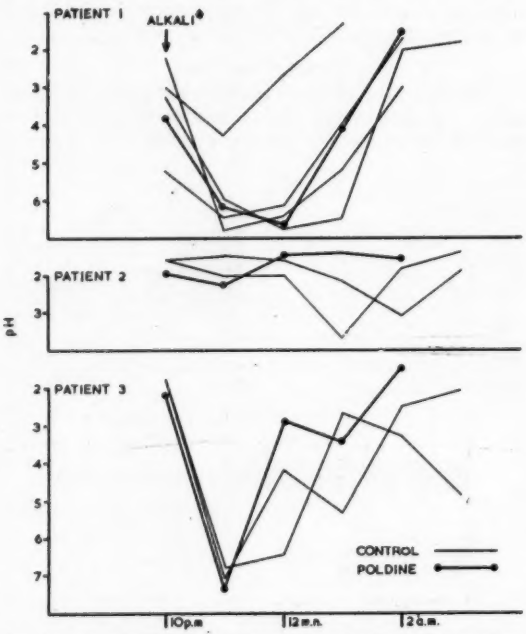

FIG. 8.—*p*H of nocturnal gastric samples in three patients after doses of alkali (mag. carb. 2.4 g. and sod. bicarb. 4 g.) at 10 p.m. with and without poldine in optimum dose.

The drugs were given in a dose of 7.5 mg. daily, divided into three doses, for the first week. Thereafter patients were seen weekly, and at each visit the daily dose was raised by increments of 7.5 mg. and later of 15 mg. daily until side-effects appeared or until a maximum of 60 mg. daily was reached. When the optimum dose or, if no side-effects appeared, 60 mg. daily was reached the trial began. The dose often needed slight alteration from visit to visit; it was increased if tolerance developed, or lowered if side-effects became severe. Table I shows that all the patients given the control tablet took 60 mg. daily, while no patient could take more than 45 mg. daily of the active tablet.

Assessment of Results

The results of treatment were judged by the following criteria:

Pain.—An effective drug should rapidly relieve pain and prevent its recurrence. Two changes were therefore noted: improvement of severe symptoms present at the beginning of treatment and the recurrence of severe symptoms during treatment.

Time Off Work on Account of Ulcer Dyspepsia.—Absence of whole days only was noted.

Barium-meal Findings.—A barium-meal examination was performed at the end of each treatment. The radiologist examined only the duodenum so as to reduce irradiation, and he reported on the presence or absence of an ulcer crater. Previous attempts to measure the size of the crater proved unreliable (C. F. Hutton, 1958, personal communication).

Patients' Preference.—Patients who completed treatment with both remedies were asked which they thought was the better.

Results

A summary of the results is shown in Table II. Eleven patients, out of 18 who entered the trial, completed treatment for three months with both active and placebo tablets. Four patients defaulted—two after the first out-patient visit, one after the third visit, and one during a severe exacerbation of pain two months after entering the trial. Three patients required admission to hospital before the trial was completed—two because of failure to control the ulcer dyspepsia as an out-patient and one for incidental illness.

The two treatments gave similar results by all the criteria used. Perhaps the most significant finding is that an exacerbation of symptoms occurred with equal frequency whether patients were receiving optimum doses of poldine or the placebo. The trial was deliberately undertaken, using alkalis for relief of pain

TABLE I.—*Details of Patients who Completed the Trial*

Case No.	Age	Sex	Length of History	First Treatment	Control			Poldine		
					Dose (mg./day)	Side-effects	Result	Dose (mg./day)	Side-effects	Result
1	34	M	2 years	B	60	None	Exacerbation	45	Dry mouth	Exacerbation
2	25	M	5 ,,	B	60	,,	Well	30	,, ,, hesitancy, constipation	,,
3	39	M	8 ,,	A	60	Dry mouth	Exacerbation	30	,, ,,	Well
4	54	M	1½ ,,	A	40–60	"Upset him"	,,	30	Dry mouth	Failed to control pain
5	37	M	1½ ,,	B	60	None	,,	15	,, ,,	Well
6	49	F	13 ,,	A	30–60	Dry mouth	Well	15	,, ,,	,,
7	25	M	8 ,,	B	60	None	Initial symptoms controlled	22·5	Very severe* hesitancy and constipation	Exacerbation
8	41	F	8 ,,	A	60	,,	Well	12	Dry mouth	,,
9	39	M	2 ,,	B	60	,,	Exacerbation	45	,, ,, hesitancy	Initial symptoms controlled
10	49	M	8 ,,	B	60	,,	,,	30–45	,, ,, blurred vision	Well
11	54	F	14 ,,	A	60	,,	Well	45	Dry mouth, hesitancy, constipation	Exacerbation

* See text for details (Case III).

only, this being the common practice. The experimental evidence already presented suggests that poldine might be beneficial if used in conjunction with large doses of alkali; this possibility has not been investigated.

TABLE II.—*Results of Treatment*

	Control	Poldine
Treatment Completed		
No. of patients	11	11
Relief of initial symptoms* within six weeks	1	1
Failure to relieve " six weeks	0	1
Exacerbation during treatment	6	5
Lost time from work	4	2
Ulcer crater demonstrated at end of treatment	7	9
Patients' preference (without preference = 2)	5	4
Treatment Incomplete		
Failure to control symptoms Admitted to hospital	1	1
Other illness Admitted to hospital	0	1
Defaulted	2	2

* Most patients were symptom-free when the trials began and only three patients were suffering pain at this time.

Observations on Side-Effects, Tolerance, and Cumulation

During the course of this study the optimum dose of poldine has been established in 14 women and 22 men.

A wide range of tolerance to the drug was noted, as shown in Table III. The side-effects complained of were those of parasympathetic inhibition, the commonest

TABLE III.—*Number of Patients for Whom the Optimum Dose of Poldine was Established in Different Dose Ranges*

Dose range (mg./day)	<10	11–20	21–30	31–50	51–75	76–100	>100
No. of patients	3	3	10	10	7	2	1

being dry mouth (26), hesitancy of urination (17), constipation (12), and blurred vision (11). Other complaints were headache (3), exacerbation of ulcer dyspepsia (3), heartburn (2), stuffy nose (2), and sore eyes (2). Dryness of the mouth was the first, or among the first, of the side-effects to appear as the dose of the drug was increased in 24 patients. The urinary symptoms were often severe; they occurred in 6 women and 11 men. Several patients developed extreme slowness in passing water, with painful distension of the bladder; complete retention did not occur. The need for caution in giving poldine to elderly men is illustrated by the following case:

Case I.—A man of 74, known to have had a duodenal ulcer for 20 years, was given a single dose of poldine, 2 mg. He complained of inability to pass water during the next six hours. Previously he had noticed slight hesitancy in starting to pass urine but had no other urinary symptoms. He was able to take large doses of propantheline without trouble.

The development of tolerance to the drug was noted in four patients, and cumulation of the drug was noted in two patients. On two occasions these effects led to unpleasant reactions:

Case II.—A man of 24 took increasing doses of poldine without side-effects until a dose of 15 mg. five times daily was reached, when he noticed slight hesitancy of micturition. The drug was stopped, and 10 days later he received two doses of 15 mg. four hours apart. Immediately after the second dose he felt very dizzy and ill, with stuffy nose, headache, and total inability to read. An exacerbation of ulcer dyspepsia began on this day. After beginning with small doses again he was able to take two 15-mg. doses as before without side-effects.

Case III.—A man of 25 noticed constipation at a daily dose of 30 mg.; at 37.5 mg. severe dryness of the mouth and hesitancy of micturition developed. The dose was reduced, and he was treated with 22.5 mg. daily for six weeks without side-effects. At the end of this time he became constipated, and developed lower abdominal pain and extreme difficulty in passing urine. He stopped taking the drug and the urinary symptoms cleared over two days. An exacerbation of ulcer dyspepsia began after this episode. In retrospect it seems likely that constipation allowed cumulation of the drug.

Discussi n

Contrary to expectation the results described do not support the hypothesis that poldine used alone is a beneficial treatment for duodenal ulcer. The apparent potentiation of the effect of alkali by poldine was not pursued further, since better results than those found with the combined treatment can be obtained by using a different regime of sucked antacid tablets without poldine (Lennard-Jones, 1960). A similar discrepancy between the reduction of acid secretion obtained with poldine under experimental conditions (Douthwaite and Hunt, 1958; Seidelin, 1960, personal communication) and the failure of the drug to reduce the acidity of gastric contents when patients take food has been observed with other drugs. For example, atropine reduces basal secretion of acid (Sun *et al.*, 1955) and the acid secretory response to a large dose of histamine (Clark *et al.*, 1960), yet atropine does not reduce the acidity of gastric contents when patients take food (Nicol, 1939; Thomson, 1958). A difference between results found under experimental conditions and results found under the conditions of clinical use can be cited for hexamethonium (Kay and Smith, 1951; Rowlands *et al.*, 1952), methanthelinium (Atkinson, 1954), penthienate bromide ("monodral") (Kirsner and Palmer, 1953; Thomson, 1958), and a long-acting form of propantheline bromide (Sun *et al.*, 1955; Kasich and Argyros, 1958; Bingle and Lennard-Jones, 1960).

There are two possible reasons why poldine and the other drugs reduce secretion under certain conditions but do not reduce gastric acidity when patients take food. Firstly, food is a powerful and natural stimulant to acid secretion; and, secondly, the acidity of the gastric contents depends on a number of factors besides acid secretion. Kay and Smith (1951) made the significant observation that hexamethonium decreases spontaneous gastric secretion but does not diminish acid secretion in response to meat extract. Observations on the effect of drugs made under basal conditions, therefore, may give little or no indication of the effect of the drug upon stimulated secretion. It is thought that the glucose test meal, used in the testing of poldine, stimulates gastric secretion mainly by distending the stomach, but this is only part of the stimulus applied during a normal meal. Food not only stimulates acid secretion but also buffers the acid produced. The acidity of the gastric contents depends on the time since food was last taken, on the nature and consistency of the food, on the amount of acid secreted, and on the rate at which food and acid leave the stomach. Most gastric antisecretory drugs tend to slow gastric emptying as well as reducing acid secretion; both factors influence gastric acidity (Rowlands *et al.*, 1952).

Controlled therapeutic trials in duodenal ulcer are difficult and time-consuming because of the remittent nature of the disease. It would be helpful if gastric antisecretory drugs could be assessed for a likely

therapeutic effect by a reliable experimental screening procedure before a controlled trial is considered. The gastric sampling technique under conditions as close as possible to those in which the drug is used clinically seems to offer such a method. Theoretically, the samples should be withdrawn from the duodenal bulb, but this is difficult technically. A tube placed in this position tends to move back into the stomach or on into the duodenum, and close radiographic control is needed. In practice, gastric sampling is probably adequate, since there is good evidence that gastric acidity parallels acidity in the duodenal bulb (Lopusniak and Berk, 1948; Atkinson and Henley, 1955). The difference, described here and elsewhere (Bingle and Lennard-Jones, 1960), between results obtained when patients take milk–cream drinks and take diet emphasizes the necessity of testing drugs under the actual conditions of use.

Summary

Poldine methosulphate, even in doses large enough to produce severe side-effects, did not reduce the acidity of the gastric contents of patients with duodenal ulcer taking a bland diet.

Gastric acidity was reduced by poldine under special conditions when patients took hourly drinks of milk–cream without other food.

Poldine apparently augmented the effect of a regime of regular antacid by day but did not prolong the effect of a dose of alkali at bedtime.

No therapeutic benefit from poldine in duodenal ulcer was demonstrated in a small controlled trial.

The relevance of these observations to the testing of other antisecretory drugs is discussed.

I thank Dr. E. N. Rowlands for much helpful advice; Miss P. Wilcox (in receipt of a grant from the Medical Research Council) for her assistance with the *p*H determinations; Dr. C. Hutton for performing barium-meal examinations; and Dr. Richard Doll for advice about the design of the therapeutic trial. I thank Dr. F. Avery Jones, Dr. K. E. Harris, Dr. J. C. Hawkesley, Dr. T. D. Kellock, Dr. E. E. Pochin, and Dr. J. F. Stokes for allowing me to study patients under their care. The dietetic departments at the Central Middlesex Hospital and University College Hospital gave much assistance by arranging the special diets. I thank Mr. V. K. Asta and Mrs. I. M. Prentice for the diagrams. C. L. Bencard Ltd. kindly supplied the "nacton" and control tablets used in this study.

REFERENCES

Atkinson, M. (1954). *Gastroenterology*, **26**, 288.
—— and Henley, K. S. (1955). *Clin. Sci.*, **14**, 1.
Bingle, J. P., and Lennard-Jones, J. E. (1960). *Gut*, **1**, 337.
Clark, C. G., Curnow, V. J., Murray, J. G., Stephens, F. O., and Wyllie, J. H. (1960). *J. Physiol. (Lond.)*, **153**, 61P.
Douthwaite, A. H., and Hunt, J. N. (1958). *Brit. med. J.*, **1**, 1030.
Kasich, A. M., and Argyros, T. G. (1958). *Gastroenterology*, **34**, 232.
Kay, A. W., and Smith, A. N. (1951). Ibid., **18**, 503.
Kirsner, J. B., and Palmer, W. L. (1953). *J. Amer. med. Ass.*, **151**, 798.
Lennard-Jones, J. E. (1960). *Postgrad. med. J.*, **36**, 722.
Lopusniak, M. S., and Berk, J. E. (1948). *Gastroenterology*, **11**, 891.
Nicol, B. M. (1939). *Lancet*, **2**, 881.
Rowlands, E. N., Wolff, H. H., and Atkinson, M. (1952). Ibid., **2**, 1154.
Sun, D. C. H., Shay, H., and Ciminera, J. L. (1955). *J. Amer. med. Ass.*, **158**, 713.
Thomson, T. J. (1958). *Clin. Sci.*, **17**, 701.

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CLINICAL EVALUATION OF POLDINE METHOSULPHATE

BY

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Assessment of the therapeutic effectiveness of an anticholinergic drug in duodenal ulcer requires experimental demonstration of substantial inhibition of human gastric secretion, confirmation of antisecretory potency under ordinary dietary conditions, and demonstration of the ability of the drug to abolish or alleviate ulcer symptoms when used on a long-term basis. The large and growing number of drugs available in this category suggests that an antisecretory drug of undoubted benefit in the treatment of duodenal ulcer has not yet been found; indeed, the real clinical value of prolonged therapy of this type has been held in question (*British Medical Journal*, 1955). Poldine methosulphate ("nacton") has been described as a selective inhibitor of gastric secretion and has been reported on favourably by Douthwaite *et al.* (1957) and Douthwaite and Hunt (1958). They studied the effect of poldine on the volume and acid content of gastric juice and observed that acid output could usually be reduced by half without troublesome side-effects appearing.

In the present investigation the clinical value of poldine has been studied by use of the following procedures: (1) inhibition of insulin-stimulated gastric juice; (2) electrometric testing of gastric juice *p*H at two dosage levels during a 24-hour period while on normal diet; and (3) long-term "double-blind" clinical trial on out-patients. All patients had radiologically proved duodenal ulcer.

Materials and Methods

Effect on Insulin-stimulated Gastric Secretion

In six fasting male patients a small-bore stomach tube was passed and the stomach emptied by hand suction. Thereafter the patient was positioned on the left side and continuous supervised mechanical aspiration was applied at a negative pressure of 5 to 10 mm. Hg. Gastric juice aspirated for the first 15 minutes was defined as the control sample. Soluble insulin 15 units intravenously was then given and gastric juice obtained for the next 45 minutes was discarded. Juice collected in the ensuing 15-minute period represented the insulin-stimulated juice, and the free-acid content of this specimen as well as of the control sample was estimated. Several days later the test was repeated, giving poldine 1 mg. intramuscularly immediately before the 15-minute collection of insulin-stimulated juice. Between the tests no treatment had been given other than modification of the diet when necessary. One patient vomited on taking his first meal after completion of the test, and this was attributed to gastric atonicity induced by poldine. A second patient felt nauseated but did not vomit. The gastric juice was titrated against N/10 NaOH using Töpfer's double indicator, and the results were expressed in milliequivalents of hydrochloric acid.

Twenty-four-hour Test of Gastric Juice pH

A Ryle tube was passed into the stomach by the nasal route in seven male patients. The tube remained in

position for 24 hours, and during this period the patient was allowed up if he wished, took "ordinary" or "bland" diet, depending on the severity of symptoms, but received no other treatment. Specimens of gastric juice were aspirated at hourly intervals. On the day after the test poldine 4 mg. was given six-hourly by mouth for five days. On the fifth day the test was repeated. A second group of seven male ulcer patients was submitted to a similar series of tests, but on this occasion the dose of poldine given six-hourly was 8 mg. Several patients in this group, though not in the first group, admitted to dryness of the mouth on direct questioning, but there were no other side-effects. Electrometric determination of gastric juice *p*H was carried out on each specimen. In a few instances the volume of juice was too small for *p*H determination and two adjacent samples were then pooled.

Clinical Trial

A "double-blind" out-patient clinical trial was conducted on 58 male subjects suffering from duodenal ulcer. In all cases a positive *x*-ray diagnosis had previously been made. Of the 58 patients, 31 received poldine tablets containing 2 mg. of the active substance and 27 received a placebo tablet of identical appearance containing lactose. Patients were allocated to poldine or placebo in random fashion by the hospital pharmacist, and neither physician nor patient knew the nature of the individual medication until the end of the trial period. The dosage of tablets was 8 to 12 daily, depending on clinical response and presence of side-effects. A supply of alkali tablets was also given to each patient, to be taken as required for the relief of ulcer symptoms. Out-patient appointments at four-weekly intervals were arranged at which clinical progress was assessed and a new supply of tablets issued. At each visit a clinical grading was made, depending on the symptomatology over the preceding four-week period as recorded by the patient on a card on which he noted, each day, symptoms as they occurred. Grading of severity of ulcer symptoms was made according to the following scale: grade 0, no dyspepsia; grade 1, epigastric discomfort, heartburn; grade 2, slight pain; grade 3, moderate pain; grade 4, severe pain, vomiting.

An exacerbation was regarded as having occurred when there was deterioration by two or more grades. The clinical grade of each patient was compared at the end of the trial with that at the outset; "improvement" was recorded if the grade had fallen by two or more, the patient was "worse" if the grade had risen by two or more, and there was "no change" if the grade varied by no more than one in either direction.

The subjects of the trial had usually been referred because of severe ulcer symptoms requiring out-patient investigation and because recent absence from work had been frequent. Social class distribution was similar in the two groups (Table I). The mean age of the patients was 45.0 years (poldine group) and 44.9 years (placebo group), and the average duration of previous symptoms was 9.5 years (poldine group) and 12.5 years (placebo group). Previous complications had consisted of haemorrhage in 15 (poldine group 8, placebo group 7) and perforation in 6 (poldine group 2, placebo group 4). The average duration of attendance for the 58 patients was 8.8 months.

TABLE I.—*Clinical Trial of Poldine Distribution of Patients by Social Class (Registrar-General Class, 1–6)*

Social Class	2	3	4	5	6
Poldine group	3	19	6	3	0
Placebo ,, ..	2	17	5	2	1

Results

Insulin Test (Table II).—Partial inhibition of insulin-stimulated acid secretion was observed in each case. The mean inhibition was 59%, and the inhibitory effect was statistically significant ($t=4.8$).

TABLE II.—*Inhibitory Effect of Poldine on Acid Response to Insulin Hypoglycaemia. Acid Output in mEq HCl. Poldine Dose 1 mg. Intramuscularly 15-minute Collection Periods*

Case No.	Resting Secretion	Insulin Secretion	Insulin Secretion + Poldine
1	1·6	6·4	3·6
2	2·5	7·6	6·3
3	0·4	5·3	1·2
4	0	2·7	0·8
5	2·8	7·0	5·9
6	0	2·6	0·7

TABLE III.—*Twenty-four Hour Gastric Juice pH Tests with Hourly Aspiration in 7 Duodenal-ulcer Patients During a Control Period, and Following Administration of Poldine Six-hourly by Mouth for 4 Days. Number of Tests in Each pH Range*

*p*H	Control	Poldine 4-mg. Doses	Control	Poldine 8-mg. Doses
1–2	124	74	75	50
2·1–3	26	45	30	53
3·1–4	9	23	19	32
4·1–5	8	6	15	16
>5	2	6	12	9

Gastric Juice pH Tests (Table III).—Since variation in dose response might occur, perhaps due to changing rates of absorption, and because it was desired to ensure that a fully adequate dose of poldine was being given, the test had been performed after four days' administration of the drug in two dosage ranges. In both series of tests there was a significant increase in the number of readings in the higher *p*H range (small dose, $\chi^2=23.4$, $P=0.1$; large dose, $\chi^2=14.9$, $P=1.0$). Even so, it will be noted that only a minority of specimens were in the *p*H range greater than 4, which is desirable if peptic activity is to be reduced to the minimum. With a Wald-type test of statistical significance (Aitchison and Silvey, 1960), the patterns of *p*H change did not differ between the small and large doses, and the latter conferred no apparent advantage.

TABLE IV.—*Results of Clinical Trial*

	Poldine Group	Control Group
Total No. of cases	31 ..	27
Improved	15 ..	8
No change	14 ..	19
Worse	2 ..	0
No. of acute exacerbations	15 ..	11
Total period of observations (months) ..	290 ..	219
Exacerbations per month of observation	0·052 ..	0·052

Clinical Trial (Table IV).—At the end of the trial the number of clinical exacerbations and the degree of clinical change, depending on the severity of symptoms, were compared in the poldine and control groups. The number of exacerbations was identical in the two groups over similar periods of observation, and the pattern of clinical change showed no significant difference between either group ($\chi^2=4.70$, $P=0.10$). No major complication occurred in any patient during the trial. One patient developed symptoms of pyloric stenosis and treatment was discontinued; it was subsequently established that he had been receiving poldine, which is contraindicated

under these circumstances. A few patients reported dryness of the mouth, but there were no other side-effects.

Discussion

There is strong evidence—for example, Woodward and Schapiro (1954)—that elimination of hydrochloric acid from the gastric juice will facilitate healing in duodenal ulcer, regardless of other possible causes. Gastric hypersecretion in this disease is due to parasympathetic overactivity, and it is rational to administer an anticholinergic drug which by inhibiting the vagal mechanism will decrease the output of acid. Additional beneficial effects result from blockade of smooth-muscle innervation, with diminution of gastro-intestinal motility. The antisecretory potency of an anticholinergic drug can best be measured in the duodenal-ulcer patient, in whom acid output is already high, and methods of doing so are numerous and varied. The effect on basal and nocturnal secretion has been studied—for example, Levin *et al.* (1948)—but, since successive tests often show wide variation in the same patient, drug effects are difficult to measure. Physiological conditions are simulated by assessing the suppressive action of the drug on secretion stimulated by a single meal; this test is regarded by Bachrach *et al.* (1954) as fully adequate for evaluation of antisecretory effect, but has the disadvantage that the drug must be given parenterally.

The secretory response to insulin hypoglycaemia is a cholinergic phenomenon mediated vagally, and the suppressive action on it of the anticholinergic drug under trial is a rational method of assessing antisecretory potency; while the conventional two-stage test permits determination of percentage inhibition, it is considered sufficient in preliminary evaluation of a drug of this type to demonstrate that substantial inhibitory potency exists. Ability of the drug to abolish or diminish acid output under histamine stimulation is a stringent test of activity, but the result has limited physiological relevance, and the effect on acid secreted under ordinary clinical conditions is the most pertinent in relation to therapeutic application. The latter can be conveniently determined by 24-hour observations of changes in acidity on normal diet while the drug is being administered.

Suggested criteria of antisecretory potency have consisted of 50 to 75% acid inhibition (Kirsner *et al.*, 1953), achlorhydria persisting for at least 30 minutes (Kirsner and Palmer, 1953), and a rise in gastric juice *p*H to 4.5 or higher (Sun and Shay, 1956). It will be noted that on 24-hour testing these criteria were satisfied by poldine to a limited degree only. Poldine given parenterally during the insulin test caused an adequate degree of inhibition which might even have been improved by adjustment of dosage and modification of the details of the test. Comparison of the drug with atropine is no longer regarded as reliable (Kirsner *et al.*, 1957) and has not been attempted. Although the antisecretory action of poldine has not been observed to be profound, under normal clinical conditions alkalis would be given simultaneously. The antimotility effect of the drug by delaying gastric emptying will permit more complete and prolonged interaction and neutralization of acid by alkalis, and is probably as important as the antisecretory action.

There is often difficulty in determining the optimal dosage of an anticholinergic drug, and it was for this reason that poldine was given at two-dosage levels in the present study. Adjustment of dosage depending on the presence and severity of side-effects is of limited value, while individual variations in pharmacological responsiveness and in rates of absorption create additional hazards in management. The many problems in clinical evaluation of the drug can be overcome by a prolonged double-blind trial which aids in elimination of these and other confusing factors; the necessary criteria for a suitable trial have been defined by Cayer (1956).

In the present study the two groups of cases were closely matched in all important respects. The control group had a longer history of ulcer symptoms, but an impression that the disease was more chronic and intractable in this group was not supported by the almost equal incidence of previous complications in the two series of patients. As decisive indices of long-term clinical effectiveness of the drug, the incidence of exacerbations of symptoms and the final clinical status may be used. Though possibly useful in relieving ulcer pain (Jones and Gummer, 1960), it has been suggested (*British Medical Journal*, 1955) that anticholinergic drugs do not affect the natural history of duodenal ulcer, and the present investigation also indicates that the long-term administration of poldine does not fundamentally alter the course of the disease.

Summary

A clinical evaluation of poldine methosulphate (nacton) in the treatment of duodenal-ulcer patients is described. Measurement of gastric juice *p*H was performed at two-dosage levels before and during poldine therapy, and the degree of inhibition effected by poldine on acid secretion stimulated by insulin hypoglycaemia was also assessed. A significant rise in *p*H or fall in acid output was noted respectively in each case. A double-blind clinical trial over a period of nine months was performed, and it was found that poldine did not significantly reduce the number of acute exacerbations or improve eventual clinical status. Side-effects were either absent or of trivial degree. It is concluded that, in company with other anticholinergic drugs, poldine, by reason of its antisecretory effect, can be usefully employed in the immediate relief of acute ulcer symptoms, but that its administration does not fundamentally alter the course of the disease.

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References

Aitchison, J., and Silvey, S. D. (1960). *J. roy. statist. Soc.*, **22**, 154.

Bachrach, W. H., Rowen, B. R., Halsted, J. A., Schapiro, H., Holmström, W., and Price, P. (1954). *Acta med. scand.*, **148**, Suppl. 288, p. 1.

Brit. med. J., 1955, **1**, 711.

Cayer, D. (1956). *Amer. J. dig. Dis.*, **1**, 301.

Douthwaite, A. H., and Hunt, J. N. (1958). *Brit. med. J.*, **1**, 1030.

—— —— and Macdonald, I. (1957). Ibid., **2**, 275.

Jones, F. A., and Gummer, J. W. P. (1960). *Clinical Gastroenterology*, p. 347. Blackwell, Oxford.

Kirsner, J. B., Ford, H., and Kassriel, R. S. (1957). *Med. Clin. N. Amer.*, **41**, 495.

—— Levin, E., and Palmer, W. L. (1953). *Gastroenterology*, **23**, 199.

—— and Palmer, W. L. (1953). *J. Amer. med. Ass.*, **151**, 798.

Levin, E., Kirsner, J. B., Palmer, W. L., and Butler, C. (1948). *Gastroenterology*, **10**, 939.

Sun, D. C. H., and Shay, H. (1956). *Arch. intern. Med.*, **97**, 442.

Woodward, E. R., and Schapiro, H. (1954). *Proc. Soc. exp. Biol. (N.Y.)*, **86**, 504.

EFFECT OF POLDINE METHOSULPHATE ON GASTRIC SECRETION OF ACID

BY

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Poldine methosulphate ("nacton") is a drug with an atropine-like action which has been described as a selective inhibitor of gastric secretion. Douthwaite and Hunt (1958) have described their experiences with it in patients with duodenal ulcer. As secretory stimulus they gave a test meal which could be expected to produce results which were probably relevant to the response to ordinary food. They showed that in patients taking adequate dosage of the drug without side-effects acid secretion could usually be reduced by half, and they demonstrated also a similar effect in normal subjects (Douthwaite, Hunt, and Macdonald, 1957).

The present paper describes the effect of poldine on the gastric secretion of acid in patients with duodenal ulcer both before and after the injection of large doses of histamine.

Material and Methods

The patients were men between the ages of 19 and 44. All gave clinical histories consistent with the diagnosis of duodenal ulcer, and this was confirmed in every case by radiography. The demonstration of either an ulcer crater or a considerable persistent deformity of the duodenal "cap," or both together, was regarded as confirmatory evidence.

Gastric Secretion Studies

The augmented histamine test (Kay, 1953) was used. It was performed exactly as described more recently (Gillespie, Clark, Kay, and Tankel, 1960). Neoplex duodenal tubes, size 16 French, with eight holes 2 by 4 mm. cut in the terminal 8 cm., were used. Figures were derived for both one hour's "basal" or "spontaneous" acid secretion and the acid output during the half-hour beginning 15 minutes after subcutaneous injection of histamine acid phosphate in a dose of 0.04 mg./kg. body weight (maximal histamine response). Results are expressed in milliequivalents of "free" hydrochloric acid.

A control augmented histamine test was carried out on all patients during the first few days of their treatment in hospital, before they received poldine. The drug was then given in four equal doses spaced evenly throughout the day, the daily dose being gradually increased until side-effects were experienced, these recurring for at least two successive days. The total dose was then reduced by as much as was required to cause these side-effects to disappear; this was usually a reduction of 4 mg. a day. Always the earliest and in most cases the only side-effect was dryness of the mouth on waking in the mornings. In two patients some temporary difficulty in starting to pass urine was experienced, and three patients noticed transient interference with visual accommodation. The total daily dose varied from 24 to 40 mg.; most patients tolerated 32 mg.

Other treatment included a liberal diet and antacids. Barbiturates were not given as a routine, nor was any preparation containing belladonna alkaloids.

Interval Between Poldine and Secretion Test

Series 1.—In 16 patients the last dose of the drug was given 11 hours before the start of the second gastric secretion test. In all these, two to three weeks elapsed between the performance of the control and the second test; this was the period required to adjust to adequate dosage without side-effects as above.

Series 2.—Six of these patients, and one other, continued to take poldine as out-patients under regular supervision, and were studied a third time after a further 10 weeks. Treatment had then been continued for a period of three months altogether. As in series 1 the last dose of the drug was given 11 hours before the second test.

Series 3.—A further group of 12 patients were treated in exactly the same way as those in series 1, except that the final dose of poldine was given by mouth two and a half hours before start of the second gastric secretion test.

It should be noted that in all these tests one and a half hours elapsed between the start of the collection of spontaneous secretion and the injection of histamine.

Results in Series 1

Table I contains data relating to spontaneous secretion and maximal histamine response in this group, before and after two or three weeks' treatment with poldine.

TABLE I.—*Series 1*

Spontaneous Secretion (11 hours after Poldine)			Maximal Histamine Response (12½ hours after Poldine)		
mEq Free HCl		% Change	mEq Free HCl		% Change
Before	After		Before	After	
5·76	7·38	+29	20·00	18·95	−5
15·21	8·41	−45	20·63	23·43	+14
0·65	2·56	+294	15·95	18·29	+15
2·06	0·51	−75	20·14	19·35	−3
4·64	2·44	−47	17·86	12·59	−29
0·00	0·57	+100	6·47	7·45	+15
10·34	11·33	+10	24·95	25·80	+3
3·83	0·94	−75	22·90	19·38	−15
10·39	6·16	−41	15·28	18·52	+21
15·70	14·07	−10	25·40	21·50	−15
7·52	7·44	−1	17·81	17·68	−1
4·54	2·59	−43	24·70	22·39	−9
7·06	1·60	−77	27·09	25·35	−6
4·57	2·44	−47	23·28	23·76	+2
1·61	4·76	+195	20·61	17·54	−15
2·14	0·60	−72	14·89	15·83	+6
96·02	73·80		317·90	307·80	

The mean secretion after poldine as a percentage of the mean secretion before poldine is 77% for spontaneous secretion and 97% for maximal histamine response.

After giving poldine the mean "spontaneous" secretion of acid was 77% of that secreted before poldine, but it is apparent from the data of Table I that the variation between subjects makes this small and inconstant reduction of no practical value. This wide variation is likely to occur particularly with spontaneous secretion, as small volumes of gastric juice of variable viscosity make recovery uncertain, in spite of the large bore of the neoplex duodenal tubes used. More consistent results can be arrived at by repeating the test many times, but this was not justifiable with an undeniably uncomfortable and lengthy procedure unless obvious technical failure was encountered.

Under the same conditions there was only a 3% mean reduction in the response to large doses of histamine (Table I). There was much less variation in the volumes collected, as the gastric aspirate after injection of histamine is usually much less viscous.

For reasons discussed below it was not thought worth while to continue these trials over a larger group in the hope of proving the significance of a small effect.

Results in Series 2

Table II contains data from patients undergoing more prolonged treatment (series 2). A small reduction in

secretion of acid was demonstrated in both spontaneous secretion and maximal histamine response (Table II). This group was studied to determine whether treatment continued for a longer period with poldine in full dosage had a more noticeable effect on acid secretion. Such a possibility was suggested by some results in the earlier work already referred to above, when after many weeks' treatment in several cases the effect appeared to persist even for some days after stopping the drug altogether (Douthwaite and Hunt, 1958).

TABLE II.—*Series* 2 (*Continuous Treatment for* 3 *Months*)

Spontaneous Secretion (11 hours after Poldine)			Maximal Histamine Response (12½ hours after Poldine)		
mEq Free HCl		% Change	mEq Free HCl		% Change
Before	After		Before	After	
7·52	15·97	+112	17·81	14·74	−17
4·54	2·28	−50	24·70	23·13	−6
7·06	2·35	−67	27·09	24·29	−10
2·14	2·41	+13	14·89	15·19	+2
4·57	3·02	−34	23·28	23·12	−1
7·49	2·97	−60	23·68	20·61	−13
1·61	0·50	−69	20·61	13·00	−37
34·90	29·50		152·00	134·00	

The mean secretion after poldine as a percentage of the mean secretion before poldine is 85% for spontaneous secretion and 88% for maximal histamine response.

A statistical analysis of the data for spontaneous secretion given in Tables I and II shows that there was a significant (1 in 20 level) reduction after poldine, even 11 hours after the last dose. However, the magnitude of this reduction is not sufficient to be of practical consequence in the treatment of patients. For this reason the drug is usually given in four doses at regular intervals throughout the day.

Results in Series 3

The results in this group of 12 patients taking poldine by mouth two and a half hours before the start of the second test are shown in Table III. With a single exception there was a considerable reduction in spontaneous secretion. After poldine the mean spontaneous secretion of acid was 33% of that secreted before the drug. The maximal histamine response was reduced in all patients, and the mean secretion after poldine was 52% of the mean of the "control" data. Both these results are significant at the 1 in 500 to 1 in 1,000 level.

Discussion

It appears, therefore, that poldine can reduce spontaneous secretion of acid in patients with duodenal ulcer. This effect is such that about three hours after taking an adequate dose of the drug, acid secretion is reduced by more than half. Eleven hours after the dose the effect is small and inconstant. Since for any hope of therapeutic benefit a considerable reduction of acid is likely to be necessary, a larger series was not examined in an effort to prove such marginal differences, though it seems likely that they exist in many patients even with this lapse of time after taking the drug.

TABLE III.—*Series* 3

Spontaneous Secretion (2½ hours after Poldine)			Maximal Histamine Response (4 hours after Poldine)		
mEq Free HCl		% Change	mEq Free HCl		% Change
Before	After		Before	After	
7·44	2·59	−65	23·40	13·19	−44
2·77	0·00	−100	20·51	1·06	−95
20·75	9·02	−57	34·96	21·95	−37
2·64	0·22	−92	25·78	13·11	−49
1·64	0·00	−100	16·83	9·66	−43
3·88	0·39	−90	29·81	19·32	−35
0·78	0·00	−100	13·55	3·24	−76
10·80	0·00	−100	13·73	4·34	−68
2·50	1·61	−36	36·48	17·18	−53
0·00	0·75	+100	8·29	4·43	−47
5·76	3·81	−34	20·00	16·01	−20
11·09	4·69	−58	11·14	9·68	−13
70·50	23·08		254·50	133·17	

The mean secretion after poldine as a percentage of the mean secretion before poldine is 33% for spontaneous secretion and 52% for maximal histamine response.

The effect on the maximal histamine response appears to be similar in its time relationships to the ingestion of poldine, and practically no effect was seen 13 hours after oral dosage; but four and a half hours after taking it a reduction by half was seen in most cases.

If series 1 and 3 are compared it will be seen that the duration of stay in hospital and all details of management were the same for both groups. The only difference between the two is in the length of the time interval between the last dose of poldine and the second test. It is reasonable, therefore, to attribute the reduction in acid secretion to the effect of poldine rather than to any other feature in the treatment of these patients.

With the use of the augmented histamine test it has been shown previously that most patients with duodenal ulcer produce about double the normal spontaneous acid secretion (Hunt and Kay, 1954). A reduction by half is therefore likely to be beneficial. Similar results after "physiological" test meals have already been mentioned above (Douthwaite and Hunt, 1958).

That poldine can reduce the acid secretion after maximal histamine stimulation is interesting. Gillespie *et al.* (1960) have shown that in a series of 23 patients with duodenal ulcer who were treated surgically by vagotomy and gastrojejunostomy the maximal histamine response was reduced considerably. If their data are treated in the same way as in this paper the mean reduction is 68%. If the presence of a gastrojejunostomy itself reduces the recovery of acid from the stomach to some extent, then it is reasonable to infer that poldine is highly or even completely effective in blocking the acid-secreting stimulus of the vagus nerves. Its particular usefulness lies in that it seems to exert this effect when taken in oral doses which do not produce side-effects.

Summary

A study of the effectiveness of poldine methosulphate ("nacton") in reducing secretion of acid in the stomachs of patients with duodenal ulcer under certain conditions is described.

The augmented histamine test has been applied before and after taking the drug.

Adequate dosage of poldine without side-effects reduced secretion by approximately one-half about four hours after taking it, and this effect had lessened considerably after 13 hours.

I am grateful to Air Vice-Marshal Sir Aubrey Rumball for supporting this work, and to Professor A. W. Kay and Mr. I. E. Gillespie for much advice and encouragement. I am indebted to Dr. J. N. Hunt for help with the arithmetic. I am grateful to the Director-General of Medical Services, Royal Air Force, for permission to publish.

REFERENCES

Douthwaite, A. H., and Hunt, J. N. (1958). *Brit. med. J.*, **1**, 1030.
—— —— and Macdonald, I. (1957). Ibid., **2**, 275.
Gillespie, I. E., Clark, D. H., Kay, A. W., and Tankel, H. I. (1960). *Gastroenterology*, **38**, 361.
Hunt, J. N., and Kay, A. W. (1954). *Brit. med. J.*, **2**, 1444.
Kay, A. W. (1953). Ibid., **2**, 77.

RINGWORM INFECTION IN A CUCUMBER GREENHOUSE

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Of infections of skin and hair by dermatophytes those caused by some of the *Microsporum* species are apt to be encountered in epidemics. Cases of which *M. gypseum* is the cause are, however, much less frequent than those caused by *M. canis* or *M. audouini*. Warren (1956) recorded epidemics of over 1,000 cases with only two examples of infection due to *M. gypseum*. La Touche (1952) recorded *M. canis* as the predominant strain in Leeds. He related this finding to the animal reservoir.

The report of the Medical Mycology Committee of the Medical Research Council (1956) does not mention *M. gypseum* as a prominent cause of ringworm and devotes attention to *M. canis*, which is known to have an animal habitat, and to *M. audouini*, which is known to spread essentially by human contact.

M. gypseum has been repeatedly isolated from soil since Vanbreuseghem and Van Brussel (1952) took advantage of its keratinophilic properties to evolve a technique for the isolation of keratinophilic fungi from soil by baiting with hair.

The present paper records, for the first time, an epidemic caused by *M. gypseum* in which the fungus was grown from soil which confirmed that infection was actually contracted from the soil itself. An epidemic was recorded by Whittle (1954) which was associated with work in a greenhouse, but the causative fungus was not isolated from the soil.

The Outbreak

In the course of a few days at the end of August, 1960, one of us (J. A.) was consulted by five patients who had ringworm of glabrous skin. Three of them had either one or two lesions, the fourth had five, and the fifth had no fewer than 27. All told a similar story of working in a cucumber house, and in fact they described their lesions as "the cucumber rash." Further, they declared that all people working in this greenhouse had similar lesions. They associated the start of the infection with a particular period of two days (August 11 and 12) when the old cucumber plants had been uprooted and discarded.

The lesions were round and up to about 1¼ in. (3 cm.) in diameter, with an entire edge, and were roughened and scaly. There was a minimal inflammatory reaction and the lesions appeared at first sight to be eczematous. They were situated on limbs, face, and upper part of the trunk. This story was told to a consultant dermatologist, who at once suggested that the lesions were ringworm due to *M. gypseum* and instanced Whittle's (1954) report.

This stimulated interest, and all who had worked in the particular greenhouse on the days in question were examined.

There were 12 people (Cases 3–14, see Table) associated with this clearance of cucumber plants from the greenhouse, and all had ringworm. Two other people (Cases 1 and 2) who had attended the growing plants had a history of typical lesions some two to three weeks before the main outbreak. One of these had actually been to the surgery with his lesion on August 11. A ringworm also occurred on the arm of the man (Case 15) who had removed the cucumber bed soil from the greenhouse on August 14.

Details of Cases

Case	Sex	Age	No. of Lesions	Skin Scrapings		Distribution
				Micro.	Culture	
Worked in greenhouse and developed lesions in mid-August						
1	M	52	2			Arm
2	M	31	1			,,
Worked in greenhouse August 11 and 12 and developed lesions at end of month						
3	M	18	2			Arm
4	F	46	1			,,
5	F	42	1			Leg
6	F	21	1			Arm
7	F	2	2			Leg
8	F	40	1			Not recorded
9	F	40	2			Arm
10	M	16	34	−	+	Face, neck, trunk, limbs
11	M	19	3	−	−	Arms
12	F	34	1	+	+	Arm
13	F	5	4	+	+	Arm, leg, trunk
14	M	7	5	+	+	Face, arm, leg, hand
Worked in greenhouse August 14 and developed lesions in early September						
15	M	30	1	−	−	Arm
Contacts of Cases 11, 13, and 14. Developed lesions in mid-September						
16	F	5	1			Leg
17	M	8	1	+	+	,,
18	M	4	1			Trunk
19	F	10	1	−	+	,,
20	F	11	1			,,
21	M	16	1	+	+	Arm
Contact of Cases 1, 11, and 21. Developed lesion in October						
22	F	45	1			Neck

Skin scrapings were taken from six of these patients, and from four of the scrapings *M. gypseum* were isolated. The skin scrapings had been examined in potash preparations in the ordinary way and had been cultured on Sabouraud's medium and on wort agar containing varying combinations of penicillin, streptomycin, and actidione. There was good growth of the dermatophyte in the positive cultures at five days.

By this time (about the middle of September) a second outbreak involving children had become evident, and *M. gypseum* was isolated from three of them. Another case occurred in October, bringing the total to 22.

Working Conditions

The cucumber plants were grown in raised beds in a greenhouse 50 by 110 ft. (15.2 by 33.5 m.). Throughout the growing season of three and a half months this house was maintained at a temperature between 70 and 100° F. (21.1 and 37.8° C.) with the necessary high humidity. Hoof-and-horn fertilizer was applied as a top dressing every five to seven days.

The cucumber compost was taken from the top 4 in. (10 cm.) of a near-by pasture. The surplus topsoil from this same pasture was stacked out of doors for use next year.

At the end of the growing season the cucumber plants were pulled up and put in a heap to rot out of doors. The soil from the raised beds was dug out and put in a separate heap also out of doors.

There were thus four possible sites for the collection of soil samples: (1) the greenhouse itself, where samples

were taken from soil on window-ledges and pipes, and also from the surface of the paths; (2) the soil from the cucumber beds that had been dumped outside; (3) the heap of rotting plants: in these an effort was made to obtain what had been surface soil—that is, the junction of stem and root with adherent soil; and (4) the surplus uncultivated pasture topsoil.

A sample was also taken of the hoof-and-horn preparation. This came from the bag that had been in use in the greenhouse. It was from a reputable firm, who stated that the raw material had been boiled for four hours, ground, and then dried to a brittle state in a steam oven.

Investigation of the Soil

An attempt was made to grow the fungus from soil samples, using human hair as a bait. The technique of Vanbreuseghem was followed in that a quantity of soil was put into a Petri dish and moistened with sterile distilled water. On to the surface of this sterilized human hair was placed and the preparations were incubated at 27° C. Within five days a good growth of fungus could be seen to be affecting the hair. In the preliminary attempts made by one of us (A. P. P.) hairs were not subcultured till the eighth day. By this time various contaminant fungi, notably of the *Penicillium* species, had made their appearance and had overgrown any possible dermatophytes.

A sample of hoof-and-horn fertilizer and 26 samples of soil from the four sources indicated above were sent to Dr. J. C. Gentles and Miss C. O. Dawson, of the department of bacteriology, University of Glasgow, who reported as follows.

Mycological Report

"The soil samples were put into Petri dishes baited with autoclaved horse-tail hair and incubated at 24° C. Those samples which were not large enough for investigation alone were bulked with another sample from the same source. In all, 10 Petri dishes of soil (four from site 1 and three each from sites 2 and 3) and one dish of hoof-and-horn meal were investigated. No growth of *M. gypseum* or other keratinophilic fungi was obtained from the fertilizer, but all 10 samples of soil yielded a heavy growth of *M. gypseum*. The dermatophyte enveloped the hair bait and could be identified within 3 to 4 days. Within 8 to 10 days small spherical structures approximately 1–2 mm. in diameter had developed. These were identified as the perfect or sexual state of the fungus recently described and named *Nannizzia incurvata* by Stockdale.* So far as we know, this is the first occasion on which *N. incurvata* has been isolated direct from soil in Britain.

"All six samples of the pasture soil surplus to requirements in the greenhouse (site 4) also yielded *M. gypseum* when incubated at 24° C. with horse-tail hair bait. In these samples, however, the growth was scanty, took longer to develop, and the sexual state was formed in only one of the six samples. The keratinophilic fungus, *Keratinomyces ajelloi*, was also isolated from four of the six samples.

"It is clear that *M. gypseum* was introduced to the greenhouse in the pasture soil and that the frequent top-dressing of the keratinaceous fertilizer, together with the prevailing conditions of temperature and humidity, resulted in rapid growth and much increased concentration of the fungus in the soil. Persons working in the greenhouse must therefore have been exposed to an abnormally heavy concentration of the dermatophyte."

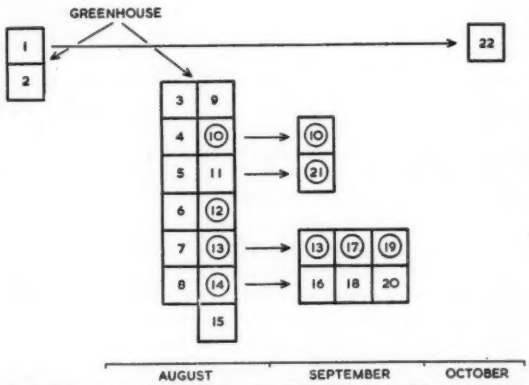
*Stockdale, Phyllis M. (1961) *Nannizzia incurvata* gen. nov., sp. nov., a perfect state of *Microsporum gypseum* (Bodin) Guiart et Grigorakis, *Sabouraudia*, 1, 41.

Epidemiology

For the sake of simplicity the patients affected have been numbered 1 to 22 (see Table). Cases 1 and 2 developed lesions in the second week in August. At the end of the same month Cases 3–15 were affected. Only Cases 1–15 had been in the greenhouse.

In the second and third weeks of September Cases 16–21 developed ringworm for the first time, and Cases 10 and 13 had second attacks. A final case (No. 22) occurred in the middle of October. The probable routes of infection are shown in the Chart.

Case 1 was the husband of Case 22; his lesions were slow to resolve, and it is felt that the wife developed her typical lesion after contact with her husband rather than from contact with her two sons (Cases 11 and 21). These sons shared a double bed, and the fungus was transmitted from 11 to 21, who had no access to the greenhouse.



Probable routes of infection. Circles indicate positive isolations on culture.

Cases 13, 14, and 10 were the children of Case 12. Cases 12, 13, and 14 were all exposed to infection in the greenhouse, and developed their lesions at the same time.

Cases 16, 17, 18, 19, and 20 were all children who played regularly with Cases 13 and 14. Case 16 was the daughter of Case 2, but it is felt that she is more likely to have caught her ringworm from her playmates, Cases 13 and 14, than from her father.

Case 7 was the daughter of Case 6.

The people infected in the greenhouse developed their lesions on the exposed parts of the body—for example, arms, necks, faces, the women's and children's bare legs, and the upper part of the trunks of the youths, who worked stripped to their waists.

Discussion

M. gypseum has been isolated from samples of soil from various parts of the world not infrequently (Zeidberg and Ajello, 1954; Frey and Durie, 1956; Stockdale, 1958). Soils from farms and barnyards in Tennessee were examined by Zeidberg and Ajello, and from these *M. gypseum* was grown. Frey and Durie examined samples of soil from parts of New South Wales and grew *M. gypseum* among other fungi. Stockdale lists *M. gypseum* among fungi grown from samples of British soil.

The above list is not exhaustive, but it serves to indicate the widespread nature of the fungus. As this

fungus is widely scattered in the soil it is all the more surprising that it has not been incriminated more often as a source of epidemic spread. A factor which possibly contributes to this state of affairs is that most studies on the epidemiology of fungus infections have been made in cities, and such infections may not be investigated when they occur in country districts. Difficulties in transport and either the necessity of sending patients a distance to hospital or unwillingness to collect appropriate samples, together with the rapid response made to treatment of infections with this fungus, all contribute. Another which is possibly applicable only in rural communities was noticed in this epidemic. Treatment of one patient was tantamount to treating several in that, once a diagnosis had been reached on one patient, a number made their own diagnosis and proceeded to share the same ointment pot. Once a patient was satisfied with his own clinical improvement the appropriate medicament was rapidly loaned out to some other group of sufferers. In the present instance this admirable community spirit certainly militated against collection of appropriate skin samples.

Although 13 patients developed lesions on their arms, only two had them on their hands, possibly because the patients washed only their hands after work. There was no history of trauma, but it is not impossible that the coarse texture of the cucumber plants could have caused mild trauma of exposed parts of the body. Under greenhouse conditions the skins were moist with sweat. Although the first lesions seen in the surgery were dry and scaly, half of the total patients had lesions which showed vesicle formation and two patients developed florid ringworms with marked inflammatory reaction. The lesions in the secondary outbreak were all minor and without inflammatory response; that is to say, the ringworms contracted by spread from patient to patient appeared to be less virulent. The two florid lesions with marked inflammatory reactions were contracted from soil.

Multiple ringworms were found only in those patients infected in the greenhouse. Untreated, the ringworms ran a self-limiting course of five to six weeks. Whitfield's ointment was effective in all cases treated.

Two months later two of the patients were seen again, and still showed some discoloration of the skin at the site of their ringworms.

Conclusion

An epidemic of ringworm infection of glabrous skin due to *M. gypseum* is described. This was originally contracted from infected soil and subsequently spread by contact.

Our thanks are due to Dr. J. G. Holmes, who originally suggested the diagnosis, and to Dr. James Gentles not only for his superior mycological skill but also for his literary ability.

REFERENCES

Frey, D. M., and Durie, E. B. (1956). *Aust. J. exp. Biol. med. Scl.*, **34**, 199.
La Touche, C. J. (1952). *Brit. med. J.*, **2**, 1081.
Medical Research Council's Medical Mycology Committee's Report (1956). Ibid., **1**, 963.
Stockdale, P. M. (1958). *Nature (Lond.)*, **182**, 1754.
Vanbreuseghem, R., and Van Brussel, M. (1952). *Ann. Soc. belge Méd. trop.*, **32**, 169.
Warren, C. M. (1956). *Brit. J. Derm.*, **68**, 264.
Whittle, C. H (1954). Ibid., **66**, 353.
Zeidberg, L. D., and Ajello, L. (1954). *J. Bact.*, **68**, 156.

STUDIES IN THE EPIDEMIOLOGY OF TINEA PEDIS

VI. TINEA PEDIS IN A BOYS' BOARDING-SCHOOL

BY

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It is generally believed that tinea pedis is a common complaint of boys' boarding-schools, yet we have been unable to find in the literature any report of a mycologically controlled survey of such a school. The community life and emphasis on sports would, indeed, lead one to expect a high incidence in these establishments. To check this, and to compare the situation with that in day-schools (English and Gibson, 1959, 1960b), we have paid two visits to a small boarding-school for boys.

The Subjects

The school catered for about 200 boy boarders aged from 7 to 18. There were no bathrooms, but all boys took morning showers twice a week and used the same shower baths after games. The school had its own swimming-bath, open in the summer only, to which organized visits were paid once or twice a week; senior boys were also allowed to use the bath in their own time. Visits by boarders to public swimming-baths were officially prohibited, but the school bath was used by 150 day-boys, who might also be using public baths.

Leather lace-up shoes were worn outdoors, light leather slippers indoors, and appropriate footwear for sports and gymnastics. Socks were always worn, but their material was not recorded.

Methods

The boys' feet were classified according to their condition into the first five groups of Holmes and Gentles (1956). Scrapings were taken from the interdigital spaces of all boys, whether they showed lesions or not, and from any lesions elsewhere on the foot, and were examined by the methods used previously in this work (English and Gibson, 1959). About 55% of the specimens were large enough for microscopical examination as well as culture.

The first visit to the school was made in October, 1958, the second eight months later, in June, 1959.

After the first visit, only the names of boys with *Trichophyton rubrum* infections were disclosed to the authorities so that treatment might be offered. All other boys, whether infected or not, continued as usual, being treated as and when they or the school authorities considered it necessary on clinical grounds alone. Unfortunately, it was impossible to obtain details of the boys so treated, but the numbers were probably small. After the second visit the names of all infected boys were disclosed.

Results

At the first visit 212 boys were seen, at the second 215: 197 of these were present on both occasions.

TABLE I.—*Incidence of Lesions and Infection According to Age*

Age	1st Visit (October)							2nd Visit (June)						
	No. of Boys	Boys with Lesions		Boys with Infection		Boys with Lesions and Infection		No. of Boys	Boys with Lesions		Boys with Infection		Boys with Lesions and Infection	
		No.	%	No.	%	No.	%		No.	%	No.	%	No.	%
7	1	0		0		0		—	—		—		—	
8	3	2		0		0		3	0		0		0	
9	5	2	34	2	17	1	9	5	3	48	0	0	0	0
10	6	3		1		1		7	4		0		0	
11	32	9		5		3		14	7		0		0	
12	30	14	47	3	10	2	7	37	18	49	5	14	3	8
13	35	18	51	6	17	5	14	35	28	80	6	17	6	17
14	37	18	49	10	27	6	16	35	26	74	8	23	6	17
15	30	22	73	10	43	7	23	36	27	75	8	22	7	19
16	21	16		8		8		23	17		6		6	
17	6	3	66	0	31	0	31	12	9	79	4	28	4	28
18	6	3		2		2		8	8		2		2	
Total	212	110	52	47	22	35	17	215	147	68	39	18	34	15

Because of the small numbers, results for boys of 11 and under have been averaged, as have those for boys of 16 and over. The incidence of lesions and of infection at both visits are shown separately in Table I, previous work by many authors having demonstrated that, in many cases, lesions of the feet cannot be attributed to fungus infection.

Lesions

The total incidence of lesions of all types increased significantly ($P<0.001$) by 16% between the two visits: the incidence of lesions increased with age at both visits. This increased incidence with age would account for part of the increase between visits, but not for the whole, as the time lapse was only eight months. Possibly the warmer weather at the second visit had some effect.

Twenty-four group IV and V lesions (fissures and vesicles) were seen—7 at the first visit and 17 at the second: of all these only three occurred in boys of 12 and under. This tendency to cracking and vesiculation at the second visit might again, therefore, be attributed either to the slightly increased age of the boys or to the warmer weather. There were 67% group II lesions and 27% group III lesions at the first visit and 58% and 29% respectively at the second.

Table II indicates the chronicity of lesions of non-fungal origin in the 142 boys who were seen at both visits but infected at neither. A minority of all boys never had lesions, but only 15% of boys of 12 and under had lesions at both visits, compared with 34% of all boys.

Nineteen of the boys who were seen at both visits, and who had both lesions and infection at the first, were clear of their infection at the second, but 15 of these still had lesions on the second occasion.

TABLE II.—*Chronicity of Lesions of Non-fungal Origin*

Age-group	Lesions at—						Total
	Both Visits		One Visit		Neither Visit		
	No.	%	No.	%	No.	%	
All boys ..	48	34	50	35	44	31	142
12 and under ..	8	15	24	44	22	41	54

Infection

Table I shows that the total incidence of infection, including lesion-free "carriers," was higher at the first visit than at the second, but this was not statistically significant: the number of boys with infections accompanied by lesions was approximately the same at both visits. This occurred despite the fact that at the second visit the boys were a little older, the weather was warmer, and the total incidence of lesions was higher. There was a tendency, which was not statistically significant, for the incidence of infection to increase with age.

The *interdigitale* type of *Trichophyton mentagrophytes* was overwhelmingly the predominant fungus in the school. At the first visit this organism was isolated from 41 boys, *T. rubrum* from four, both fungi from one, and one boy was microscopically positive only. At the second visit *T. mentagrophytes* was isolated from all the infected boys except two, who were microscopically positive only.

Lesion-free "Carriers"

At the first visit 11 boys with no lesions were found to be harbouring a dermatophyte. When these boys were examined at the second visit six were free of infection though three of them had developed lesions; four remained infected and had developed lesions; and only one was still in the "carrier" state. All "carriers" at both visits were boys of 15 and under.

Recovery

It has been stated that boys infected with *T. mentagrophytes* at the first visit were not told of their condition. Of these boys 40 were seen again at the second visit,

TABLE III.—*Recovery in Boys Infected with T. mentagrophytes*

Age	No. Infected			No. Recovered	
	With Signs	"Carriers"	Total	No.	%
12 and under	7	4	11	11	100
13 „ over	22	7	29	10	34
All ..	29	11	40	21	52

and Table III shows that, by then, all 11 of those of 12 years and under had recovered, but that this was true of only 10 (34%) of the 29 over 12 years old. These figures suggest the possibility of a certain resistance to the disease in the younger boys.

Comparison with Day-schools

Results for 11–14-year-old boarders can be compared with those for day-boys in local authority senior schools, obtained at a previous survey (English and Gibson, 1959), though there will be a very slight discrepancy in age (English and Gibson, 1960b).

The total incidence of lesions at the first boarding-school visit was very similar to that in day-schools; at the second visit it was significantly higher ($P<0.001$). It may be noted that this second boarding-school visit was the only one in any school carried out in summer.

There was also a much higher incidence in the boarding-school, at both visits, of vesicular and erythematous lesions and of cracking.

The incidence of infections accompanied by lesions in the comparable age-group in the boarding-school, constant at 12% at both visits, was nearly double the

TABLE IV.—*Comparison of 11–14-year-old Boarders with Boys from Local Authority Day-schools (English and Gibson, 1959)*

	Boarding-school		Day-schools
	1st Visit	2nd Visit	
% lesions	43	65	40·3
,, infection and lesions	12	12	6·6
,, "carriers"	6	3	1·5*
,, group III, IV, and V lesions out of total lesions	27	45	10

* Estimated from a sample taken from a school with 8·9% infection. No "carriers" were found in a school with 2·2% infection.

average in the day-schools and compares with a 9% incidence in the most highly infected day-school. The percentage of "carriers" in this day-school was also very much lower than in the boarding-school.

Discussion

The high incidence of tinea pedis in this boarding-school supports the ideas put forward in a previous article (English *et al.*, 1960) regarding factors of seed and soil in cross-infection. The boys' footwear, like that of pupils of day-schools, was of a type which would be likely to render their feet suitable soil for fungal growth: their communal life would offer many more opportunities for the dissemination of the organisms than would be the case with day-boys. This combination could be expected to result in a higher infection rate than in day-boys. It is also possible that more boarders than day-boys come to school having already contracted the infection in their families, for pupils in boarding-schools are drawn from higher social classes than those in local authority day-schools and there are indications that the risk of cross-infection is greatest in families of high social class (English and Gibson, 1960a).

"Carriers"

Most workers have found lesion-free "carriers" in populations they have surveyed, and various guesses regarding their significance have been made (Ajello *et al.*, 1945; Sulzberger and Baer, 1955). No one, apparently, has re-examined these people to find out the fate of their infections, though Marples and Chapman (1959) suggested this course, and Strauss and Kligman (1957) mention such a study without giving details. We have been able to follow up 11 "carriers" and to show that only one still carried the fungus on lesion-free feet eight months after the initial examination. We therefore believe that true carriers of tinea pedis are rare: in most cases we are probably dealing with incipient or resolving infections, not with the true carrier state where "host resistance is preventing clinical manifestation" or where "the fungus is a saprophyte" (Holmes and Gentles, 1956).

Rosenthal *et al.* (1956) believe that cross-infection is not important in clinical disease, but that such disease occurs when a dermatophyte, carried on the feet of most people, becomes active because "soil" conditions become suitable. If so, one would expect an approximately equal incidence of "carriers" in all communities of similar age-group. In fact we have shown, by comparing boarding and day-boys, that the "carrier" rate rises with the incidence of visible infections, an observation that is compatible with the idea that in most cases "carrying" is merely a stage in a clinical infection.

Lesions and Infection

So many workers in so many parts of the world have reported that the presence of lesions in the toe-webs does not necessarily indicate fungous infection, that we feel that this must now be accepted as fact. As to whether the presence of lesions of non-fungal origin predisposes to fungal infection (Meenan, 1953; Marples and Chapman, 1959), the evidence is far more conflicting. That the overall incidence of lesions in a community is in no way related to the infection rate is shown by comparing our two visits to the boarding-school, where lesions but not infection rose in the summer, and also by comparing the day-schools with each other (English and Gibson, 1959).

If lesions, in themselves, predispose to infection one would expect to find that boys with persistent lesions were particularly prone to tinea pedis. Yet 34% of boys in this school had lesions at both visits but fungal infection at neither. Figures for 56 uninfected boys from local authority day-schools who were examined three times over a period of two years are also of interest in this connexion. Of these, 8 (14%) had lesions on all occasions, 30 (54%) had them at one or two of the examinations, and only 18 (32%) were free of lesions during the whole period.

On the other hand, the tendency in boarders for both lesions and infection to rise with age might indicate that lesions can predispose to infection, particularly as both persistent lesions and persistent infection were far less common in younger boys.

The high recovery rate in the younger boarders suggests the possibility of a certain resistance to infection not present in older boys. If this is indeed so, it might well be due to the better condition of the feet of the younger boys as indicated by fewer and less persistent lesions, and our suggestion (English and Gibson, 1959) that low infection rates in younger children are due entirely to the shorter exposure to risk must be modified.

It is clear from the above that there is no single, direct relationship between lesions and infection, but some connexion probably exists. Possibly the coexistence of lesions with some other factor or factors unknown is crucial.

Summary

The pupils of a boarding-school catering for about 200 boys were examined for tinea pedis on two occasions, with an eight-months interval between. At the first visit 52% of the boys had lesions and 22% were infected with dermatophytes; at the second visit 68% had lesions and 18% were infected. The *interdigitale* type of *Trichophyton mentagrophytes* was the most important causal fungus, but *T. rubrum* was also isolated at the first visit. The situation is compared with that in local authority day-schools visited previously.

Of 11 lesion-free "carriers" seen at the first visit only one was still carrying the fungus on lesion-free feet eight months later: this suggests that true carriers are rare, the majority of such cases representing either incipient or healing infections.

The relationship to fungal infection of lesions of non-fungal origin is discussed, and it is concluded that, though such lesions may sometimes predispose to fungal infection, other, unknown, factors are also involved.

We are grateful to Dr. C. Bernard for his assistance with this survey. We acknowledge the kindness of the headmaster in allowing us to visit his school, and of the matron for her ready co-operation during our visits. We are indebted to Miss E. H. L. Duncan, of the Central Health Clinic, Bristol, for statistical help, and to Mr. G. A. Wills for technical assistance.

REFERENCES

Ajello, L., Keeeney, E. L., and Broyles, E. N. (1945). *Bull. Johns Hopk. Hosp.*, **77**, 440.
English, Mary P., and Gibson, Mary D. (1959). *Brit. med. J.*, **1**, 1442.
—— —— (1960a). Ibid., **1**, 1860.
—— —— (1960b). Ibid., **2**, 577.
—— —— and Duncan, Ethel H. L. (1960). Ibid., **2**, 573.
Holmes, J. G., and Gentles, J. C. (1956). *Lancet*, **2**, 62.
Marples, Mary J., and Chapman, Eileen N. (1959). *Brit. J. Derm.*, **71**, 413.
Meenan, F. O. C. (1953). *J. Irish med. Ass.*, **33**, 102.
Rosenthal, S. A., Baer, R. L., Litt, J. Z., Rogachefsky, H., and Furnari, Domenica (1956). *J. invest. Derm.*, **26**, 41.
Strauss, J. S., and Kligman, A. M. (1957). *Arch. Derm. (Chicago)*, **76**, 70.
Sulzberger, M. B., and Baer, R. L. (1955). *Yearbook of Dermatology and Syphilology, 1954–5*, p. 9. Chicago.

STUDIES IN THE EPIDEMIOLOGY OF TINEA PEDIS

VII. THE CIRCULATION OF INFECTION

BY

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> "In recent years there has been increasing recognition that although there may be specific and necessary causes of certain diseases, these do not provide a complete account of causation. A whole network of circumstances, inherited and environmental, determine the genesis, course, and effects of disease."—Lord Cohen of Birkenhead, *The Observer*, March 6, 1960.

Previous articles in this series (English and Gibson, 1959a, 1959b, 1960a, 1960b; English *et al.*, 1960, 1961) have shown that the incidence of tinea pedis varies in different communities situated in the limited geographical area of the City of Bristol and its immediate surroundings. Evidence has been put forward that this variation is largely due to differing opportunities for contact with an exogenous source of infection.

This is contrary to the views of Sulzberger and Baer (1955), who believe, as do many other workers who adhere to their school of thought, that "tinea pedis is not transmissible in the ordinary sense." These authors, putting forward what might be called the "flare-up" theory, state that "there is much evidence that in parts of the world where tinea pedis is prevalent, many, if not most, *grossly uninfected* subjects actually do carry fungi here or there on the feet" (p. 12, their italics), and they argue that whether or not clinical disease results depends on the personal resistance of the subject. They give no details of the evidence they mention. Yet a few lines earlier, in the same article, they have written, "One of the most instructive of the recently acquired facts is the observation that the skin of most *human beings free from clinically active tinea pedis appears to have a remarkable ability to rid itself of fungi*, even when exposed to relatively massive, not to say overwhelming, quantities under experimental conditions" (p. 12, their italics). Their own experimental work (Baer *et al.*, 1956) and that of Strauss and Kligman (1957) support this latter statement.

Baer *et al.* soaked one foot of each of 54 subjects in a footbath containing a suspension of *Trichophyton mentagrophytes* and examined scrapings from these feet at weekly intervals for the next six weeks. They were able to re-isolate the fungus from only one subject, though they obtained microscopically positive scrapings from a further 26. This extraordinarily high rate of failure to grow the fungus from subjects who were microscopically positive (and who presumably were not using fungicides) suggests that most of the fungal elements seen were no longer viable. The sporadic nature of the microscopical evidence is also strange: of the 26 subjects whose exposed feet were microscopically positive, 18 were positive at only one of the 6 examinations; and of the 8 who were positive more than once, only 3 were positive in two successive weeks. In addition, of all the 26, only 8 were positive in the first week after exposure.

The authors do not state whether their subjects were asked to take any precautions against infecting themselves from outside sources during the follow-up period. If this was not done, such extraneous infection might well account for their isolation from the exposed feet of two of the subjects of dermatophytes other than *T. mentagrophytes*, and possibly also for some of the sporadic positive microscopical results from both exposed and control feet.

Sulzberger *et al.* (1942) found that tinea pedis and cruris very rarely spread in families, and this work is used by Sulzberger and Baer (1955) as further evidence of the lack of importance of transmission as a cause of clinical disease. The inadequacy of the methods used to obtain these results has been discussed elsewhere (English, 1957; Many *et al.*, 1960).

Strauss and Kligman (1957) placed massive inocula in the interdigital spaces of persons with clinically normal feet and subjected the feet to treatments designed to produce warm, moist conditions over long periods of time. Even with such extreme methods they state that "most infections were transient, and usually fungus elements were found on only one or two (subsequent) weekly examinations." Infections were not induced by imposing warm, moist conditions on normal uninoculated feet.

Clearly a subject with an inherent resistance to tinea pedis will not contract the disease *despite* the fact that he has been in contact with it: that he will continue to carry the fungus on lesion-free feet over long periods seem most unlikely, on the available evidence, in more than a very small percentage of cases. For a subject with temporarily or permanently lowered resistance tinea pedis is transmissible: he may contract the disease if, *and only if*, he has recently been exposed to it. This is the only reasonable explanation for differing infection rates in communities of similar types.

Factors Determining the Incidence of Tinea Pedis

The ideas put forward in the present article, based on findings in Bristol, serve only to underline the results of Gentles and Holmes (1957) in their careful investigation

of tinea pedis in coal-miners, and to support their closely argued conclusions that tinea pedis is a transmissible disease.

The most important factors determining the incidence of tinea pedis are: (1) the presence of inoculum in places in which the bare foot may come into contact with it; (2) the frequency and duration of exposure of the foot to the inoculum; (3) the susceptibility of the foot once inoculation has taken place, depending on personal resistance to infection, the condition of the foot, the type of footwear, etc. (susceptibility in any one person may vary from time to time); and (4) the species of dermatophyte and any variation in virulence.

The interaction of these four factors determines whether or not an individual, at any given time, will contract tinea pedis, and will therefore also determine the level of infection in the community to which that individual belongs. The existence of a very small number of true carriers does not affect the general picture.

The relative importance of the factors varies in different communities according to their customs and conditions of life, whether these are voluntary or imposed by circumstances or authority. It is this varying interaction that explains differences in incidence in the various communities, and also in the same community at different times.

The present lack of knowledge concerning host resistance and fungal virulence largely precludes the study of the epidemiology of tinea pedis from these points of view. But this does not prevent the elucidation of those aspects of the problem which depend on exposure to infection. This is what has been attempted in this series of studies, although a few indications of the factors affecting host resistance—for example, sex and footwear—have also been obtained.

With some exceptions (Gentles and Holmes, 1957; Lesun, 1958; Cremer, 1958, 1959) mycologically controlled surveys of tinea pedis consist of single visits to specific residential or working groups, or of reports on incidence from hospital clinics; seldom have a number of surveys been made in the same locality at close time-intervals. The resulting epidemiological picture is incomplete and gives little idea of the continuity of circulation of this infection. By studying different groups of people in a limited geographical area, and by visiting some of them more than once, it has been possible to discover, for Bristol, the ways in which tinea pedis is most usually spread, and so to deduce the risk of infection run by individuals at different times in their lives.

Circulation of Infection in the Bristol District

The marked difference in the incidence and distribution of the two species of *Trichophyton* principally involved is sufficient evidence of differences in their epidemiology to warrant their separate treatment. *Epidermophyton floccosum* occurred so infrequently that useful comment is not possible.

In all that follows, statements for which no specific reference is given have been discussed in previous articles in this series. Numerical relationships used in the diagrams are either those obtained during the surveys or are reasonable deductions from them.

Obviously the conclusions reached can only be general ones, and the diagrams do not represent the *only* routes of cross-infection in the given circumstances, but merely the *most usual* ones. For instance, cross-infection with *T. rubrum*, both in the armed Forces and at swimming-baths, undoubtedly occurs (Gentles (1956) has isolated this fungus from the floor of a pit-head bath), so does cross-infection with *T. mentagrophytes* among girls, but, compared with other routes, they are not of sufficient importance to be included in the relevant diagrams.

T. mentagrophytes (interdigitale Type)

This fungus is by far the most common cause of tinea pedis in Bristol. In boys aged 11–14 years in local authority day-schools the incidence of infection is about 6.5%, and cross-infection usually takes place at the local swimming-bath. In a boarding-school, on

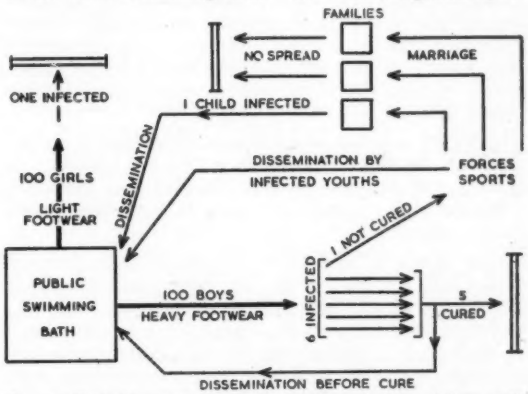

FIG. 1.—Probable route and extent of dissemination of tinea pedis due to *T. mentagrophytes* in males and females of families whose children attend local authority day-schools (mainly social classes III, IV, and V, some of class II).

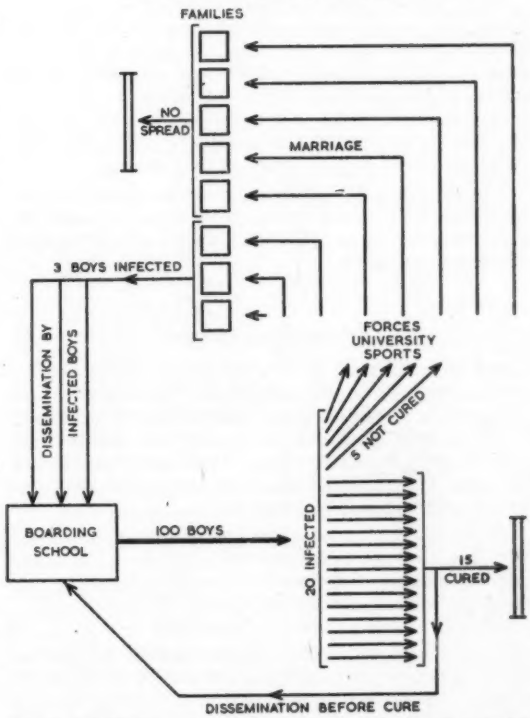

FIG. 2.—Probable route and extent of dissemination of tinea pedis due to *T. mentagrophytes* in males of families whose sons attend boarding-schools (mainly social classes I and II).

the other hand, the incidence in boys of the same age was about 12%, a level which can be attributed mainly to communal life and an emphasis on sport.

Day-school boys seldom contract an infection from their families. No figures are available for boarding-school boys, but the high cross-infection rate in families of high social class, from which boarding-school pupils are drawn, suggests that these run more risk in their families than do day-school boys. From his childhood, therefore, the average boy of social class III, IV, and V (Registrar-General's social classification) is likely to run less risk of infection with *T. mentagrophytes* than a boy from class I or than many from class II.

Proportionately more boys from the higher social classes than from the lower attend universities. Marples and di Menna (1949) and other workers have shown that the incidence of tinea pedis among students is high, especially in those living in hostels. Here again, therefore, boys from the higher social classes run a greater risk of infection.

Grammar schools have not been investigated, but the incidence in them could reasonably be supposed to approximate to that in other day-schools, though it might be raised somewhat owing to the higher social class of the pupils.

Tinea pedis in girls attending day-schools averages 1.6% and is therefore far less common than among boys. No direct information about girls' boarding-schools is available, but the ratio of 2:1 infected males to females in families suggests that girls are indeed less liable to be infected with *T. mentagrophytes* than boys and that the incidence in girls' boarding-schools might also be low. Girls of all social classes, therefore, seem less likely to be infected than boys.

After leaving school, many more boys than girls join sports and swimming clubs, and, up to the time of writing, all boys have been subject to national service with the armed Forces. These are all situations in which cross-infection with tinea pedis is likely to take place (Hopkins *et al.*, 1947; Tritsmans and Vanbreuseghem, 1955). As young adults too, therefore, males run more risk of infection than females.

The foregoing discussion can be summarized in two diagrams (Figs. 1 and 2) which illustrate the probable way in which tinea pedis due to *T. mentagrophytes* circulates in Bristol.

Trichophyton rubrum

The low incidence of this fungus in all schools and in a sample of the adult population (Warin, unpublished evidence) indicates that there is still too small a reservoir of infection in Bristol for it to cause a major outbreak of tinea pedis in communities. This is not true of other countries (Scheffler, 1958) or of all communities in Britain (Gentles and Holmes, 1957).

There are two main sources of new cases in Bristol. The first, and probably the most important, is cross-infection within the family. Though apparently not highly infectious, the disease caused by this fungus is usually far more resistant to treatment than that due to *T. mentagrophytes*, so that members of a family in which there is an infected person are exposed to constant risk over a long period.

Secondly, a considerable number of cases are not attributable to indigenous cross-infection at all, but, as is made clear by patients' histories, to infections contracted during residence abroad and imported *de novo* into Britain.

Evidence from all sources in Bristol and from Scheffler (1958) in Germany supports the idea that, unlike *T. mentagrophytes*, *T. rubrum* can attack females almost as readily as males.

Information regarding the effect of social class on the incidence of *T. rubrum* is scanty. That it occurred no more often in the boarding-school than in the day-schools suggests that it is not particularly associated with any social group, and this may well be true at present, after a war in which large numbers of all classes have served abroad. But a very much higher proportion of members of the professional classes than of the working classes are employed abroad in peacetime, and this, coupled with the possibility suggested by the family survey of a higher cross-infection rate in professional families, should ensure that *T. rubrum*, as well as *T. mentagrophytes*, will eventually have a higher incidence in the upper classes.

The surveys on which this reconstruction was based were carried out before the introduction of oral therapy with griseofulvin. The success of this drug offers some hope of breaking the chain of infection (see Fig. 3).

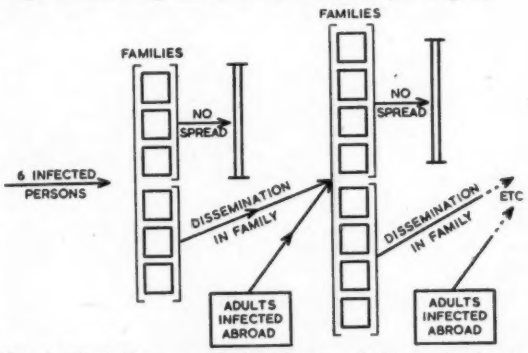

FIG. 3.—Probable route of dissemination of tinea pedis due to *T. rubrum* in both sexes and in all social classes.

The incidence of *T. rubrum* as a cause of tinea pedis in this country has been increasing steadily for many years. If, despite griseofulvin, this trend continues, residential communities, swimming-baths, and communal washing facilities will become relatively more important foci of cross-infection as the total number of cases rises. Circulation diagrams for this species will then increasingly resemble those for *T. mentagrophytes*, except that a larger proportion of females are likely to be affected.

Relevance to Other Localities

The foregoing discussion, and the diagrams evolved from it, apply specifically to Bristol. What is their relevance elsewhere? Fig. 1 could be expected to apply to most British cities and towns with public swimming-baths. But since the baths are one of the main foci of cross-infection it would not be a true picture for country districts (Amrein, 1953) too far from the baths for children to use them frequently. A very low infection rate would be expected in such conditions, though the disease would be kept in existence by returning national service men. With the ending of national service it is probable that the incidence of tinea pedis due to all fungi will gradually decline over the whole country.

Fig. 2 shows the boarding-school and the family as the main sources of cross-infection; Fig. 3 the family and residence abroad. These sources are not primarily dependent on local amenities, so the diagrams could be expected to apply to the appropriate sections of the population in any part of the country.

None of the diagrams would be true for towns or districts of Britain where a high proportion of the population is engaged in a single employment involving particular risks; for instance, mining communities. Here the main source of infection is the pit-head bath, and the high incidence in the miners themselves (Gentles and Holmes, 1957) would be expected to lead to an abnormally high incidence in their families and in the schools.

Finally, it must be stressed that many of the ideas put forward in this article are only deductions from the observed facts, and further surveys of specific sections of the population would be necessary to verify them.

Summary

The relative importance in attacks of tinea pedis, of flare-ups of latent endogenous infections, and of recent contact with exogenous sources of infection is discussed. It is concluded that the great majority of such attacks can be attributed to contact with infection from an outside source. If this is true, it should be possible to determine the routes by which tinea pedis is most usually circulated in any given locality. Such routes are suggested for the *interdigitale* type of *Trichophyton mentagrophytes* and for *T. rubrum* infections in Bristol and its immediate surroundings, and their applicability to other localities is discussed.

I am indebted to Dr. G. A. J. Ayliffe, of London, to Dr. R. P. Warin and Dr. C. D. Evans, of Bristol, and to Dr. J. C. Gentles, of Glasgow, for discussions and criticism during the preparation of this article.

REFERENCES

Amrein, H. P. (1953). *Praxis*, **42**, 197.
Baer, R. L., Rosenthal, S. A., Litt, J. Z., and Rogachefsky, H. (1956). *J. Amer. med. Ass.*, **160**, 184.
Cremer, G. (1958). *Ned. T. Geneesk.*, **102**, 1540.
—— (1959). Ibid., **103**, 448.
English, Mary P. (1957). *Brit. med. J.*, **1**, 744.
—— and Gibson, Mary D. (1959a). Ibid., **1**, 1442.
—— —— (1959b). Ibid., **1**, 1446.
—— —— (1960a). Ibid., **1**, 1860.
—— —— (1960b). Ibid., **2**, 577.
—— —— and Duncan, Ethel H. L. (1960). Ibid., **2**, 573.
—— —— and Warin, R. P. (1961). Ibid., **1**, 1083.
Gentles, J. C. (1956). *J. clin. Path.*, **9**, 374.
—— and Holmes, J. G. (1957). *Brit. J. industr. Med.*, **14**, 22.
Hopkins, J. G., Hillegas, A. B., Ledin, R. B., Rebell, G. C., and Camp, E. (1947). *J. invest. Derm.*, **8**, 291.
Lesun, L. G. (1958). *Sborn. Rab. I. Vseross. Konf. Vrach. Derm.-Venerol. (Moskva)*, p. 56. Abstracted in *Abstr. Sov. Med.*, 1960 (Part B), **4**, 618.
Many, H., Derbes, J., and Friedman, L. (1960). *Arch. Derm. (Chicago)*, **82**, 226.
Marples, Mary J., and di Menna, Margaret E. (1949). *Med. J. Aust.*, **36** (ii), 156.
Scheffler, H. S. F. (1958). *Mykosen*, **1**, 102.
Strauss, J. S., and Kligman, A. M. (1957). *Arch. Derm. (Chicago)*, **76**, 70.
Sulzberger, M. B., and Baer, R. L. (1955). *Yearbook of Dermatology and Syphilology, 1954–5*. Chicago.
—— —— and Hecht, R. (1942). *Arch. Derm. Syph. (Chicago)*, **45**, 670.
Tritsmans, E., and Vanbreuseghem, R. (1955). *Belg. T. Geneesk.*, **11**, 625.

Medical Memoranda

Meningitis due to a Soil Organism after Penetrating Injury of Pharyngeal Wall

The remarkable nature of the following case seems to be sufficient reason for putting it on record.

CASE REPORT

On March 23, 1959, a boy of 12 years was engaged in throwing a bayonet, dating from the 1914–18 war, and weighing 15 oz. (425 g.), against a tree-trunk, when the bayonet glanced off and entered the open mouth of his younger brother, aged 10. The point pierced the posterior pharyngeal wall and embedded itself in the cervical spine, whence it had to be pulled out with some force.

When admitted to hospital the boy was somewhat shocked and complained of dysphagia. There was a small superficial cut of the dorsum of the tongue, and a minute chip off the margin of the second upper right incisor tooth. A vertical laceration about ¾ in. (2 cm.) long in the posterior pharyngeal wall was gaping slightly, but no attempt was made to suture it. A.T.S. and prophylactic penicillin were given.

During the next 24 hours the boy became progressively more and more drowsy, and complained of severe frontal headache. Neck rigidity was marked and Kernig's sign strongly positive. Lumbar puncture yielded turbid blood-stained fluid. A combined regime of parenteral streptomycin and penicillin and oral sulphadiazine was instituted, and after a further 24 hours his condition rapidly improved. A week after onset, all signs of meningeal irritation had disappeared, and the pharyngeal wound had healed. The boy was discharged fit two weeks later.

The cerebrospinal fluid was found to contain numerous pus cells and occasional Gram-negative bacilli. These proved sensitive to all the antibiotics given. The final laboratory report stated that the organism grown was none of the known pathogens, but had the characteristics of one of the nitrifying soil bacteria. These organisms run into many thousands, and have never been fully classified, so it is not surprising that the one isolated could not be identified with any of the known types.

X-ray films of the cervical spine showed no bony injury. From a study of the films and from examination of an articulated skeleton it was evident that the bayonet tip must have pierced the meninges in one of two places—either beside the odontoid process of the axis vertebra or through the articulation of the atlas vertebra with the skull.

COMMENT

The possibility of such an occurrence must indeed be very remote. A slightly greater degree of force would have resulted in sudden death. To complete an unusual combination of circumstances, the tip of the bayonet must have carried into the meninges a soil organism which then became pathogenic. A search in the literature has so far revealed no comparable case.

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The 1961 edition of the International Planned Parenthood directory, *World List of Family Planning Agencies*, is now available from the IPPF, 69 Eccleston Square, London S.W.1, price 2s. 6d. a copy. The directory contains the latest population figures and information on family planning services in fifty-seven countries.

Reviews

HUMAN EMBRYOLOGY

Essentials of Human Embryology. By Frank D. Allan, M.S., Ph.D. (Pp. 225+xiii; illustrated. 40s.) New York: Oxford University Press. 1960.
A Textbook of Human Embryology. By R. G. Harrison, M.A., D.M. (Pp. 244+xi; illustrated. 45s.) Oxford: Blackwell Scientific Publications. 1959.

These two volumes raise wider problems than those involved in a conventional review. They need to be seen against the background of changing trends in the field of medical education, where increasing efforts have been made to reduce the content of the medical curriculum more especially in the preclinical subjects. The two books now before us represent an attempt to achieve this in the case of embryology. Professor Allan states his aim clearly and unequivocally. Professor Harrison informs us that it is pure coincidence that his book is appearing at the present time, when the medical curriculum is under almost continuous review. His main objective is the elimination of "much detail of morphological embryology," in order to place the accent on function, though he hopes, none the less, to assist the understanding of adult human anatomy. Both books possess undoubted merits, but according to the angle from which one regards medical education might also be regarded as exhibiting serious defects.

It is easy enough to stress the necessity for condensation, and to point out that it arises from a progressive increase in the amount of information which the medical student is expected to acquire. It is very much more difficult to decide how far this condensation should go, or precisely how it should be effected. One way of doing so is to present the student with a greatly reduced number of bare facts. He learns these facts, but is unable to appreciate either how they were ascertained or how they might be critically assessed. Herein lies the fundamental difference between a university education and one which is purely technical or vocational. In the university knowledge is studied from its foundations, and he who has approached it in this manner may himself be able to add to it at a later date.

Professor Allan adopts the vocational method. He writes in his introduction: "It should be realized that in a book of this nature many generalizations have been made, and discussions of most controversial issues have been avoided." If one accepts the validity of such an approach Professor Allan's book must be regarded as reasonably satisfactory for the purpose of learning embryology, provided that it is adequately supplemented by lectures and practical work. Its mode of presentation, resembling that of the Students' Aid Series, makes it particularly suitable for rapid factual revision.

Professor Harrison's book has a completely different outlook. He repeatedly touches on controversial issues and their possible implications. Consequently the book is both interesting and stimulating. But to do this and yet appreciably shorten the work means that much must be left out. This indeed raises one of the major problems of curricular revision—namely, what constitutes unnecessary detail. Most teachers will undoubtedly feel that in this instance neglect of morphological considerations has been carried too far in some respects, not far enough in others. Thus there is no general account, however brief, of the growth of the embryo as a whole, and of the main changes in external form throughout foetal life. This is an omission which should be rectified in future editions. On the other hand, there are three illustrations of the inguinal canal in the adult male in various stages of dissection.

If one were compelled to choose between these two books, one would probably select that of Professor Harrison because of its more stimulating outlook, but ensure that it, too, should be supplemented by additional teaching.

Incidentally, why "Syncitium"?

J. M. YOFFEY.

ADVANCES IN GENETICS

Recent Advances in Human Genetics. Edited by L. S. Penrose, M.A., M.D., F.R.S. With the assistance of Helen Lang Brown. (Pp. 194+vii; illustrated. 27s. 6d.) London: J. and A. Churchill Ltd. 1961.

With the rapid progress made in human genetics it is appropriate that Professor Penrose should sum up "recent advances," and this book is highly recommended for those with some genetical knowledge. Given this, there are very clear and useful expositions on subjects of interest to physicians—particularly to the paediatrician, the endocrinologist, and the medical officer of health.

An outstanding contribution is that on the chromosomes (D. G. Harnden), which embodies all the new work on the subject, and it makes for clarity to have this chapter separated from developmental sex abnormalities, a complicated subject concisely dealt with by O. J. Miller.

J. H. Renwick sums up very comprehensively what is known on linkage in Man. For the clinician, he gives especially useful advice on the choice of material for genetic studies, including the avoidance of "inadequate markers." He has some interesting suggestions for further work, and points out that, if a trisomic individual, such as a mongol, of blood group AB were found to have an AB and an O parent, one would know that the ABO locus was situated on the trisomic chromosome. He also speculates interestingly on the possibility of detecting mitotic crossing-over in human tissue culture cells. This would enable the linear order of the genes to be identified as has been done on a large scale in micro-organisms.

Penrose himself discusses the genetics of growth and the development of the foetus, summarizing the recent information that is available on common malformations and stressing that many of them may have different causes in different individuals, and that there are no simple genetic rules applicable to all of them.

C. A. B. Smith's section on statistical theory is written for comparatively ordinary people and not for mathematicians. He gives a new and comprehensible method for testing segregation ratios, and his chapter also explains many of the methods the names of which are constantly appearing in papers dealing with genetic analysis.

There is an admirable chapter on the abnormal haemoglobins by Park Gerald; otherwise Penrose does not cover the subject of biochemical genetics at all, but refers the reader to well-known treatises such as Harris's excellent *Human Biochemical Genetics*. It is a pity, with the wealth of talent at his disposal, that he has not dealt with what is after all one of the corner-stones of genetics, and on which there is a great deal of recent

information. There is, however, so much of value in the book and so much information contained in a small space that it seems churlish to complain about this one fault.

C. A. CLARKE.

DISORDERS OF LIPOID METABOLISM

The Dyslipidoses. By Raul Fleischmajer, M.D. Foreword by Marion B. Sulzberger, M.D. (Pp. 509+xvi; illustrated. £6 8s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

This is a valuable monograph on the disorders of lipoid metabolism. The subject is a difficult one, but it is discussed in a lucid manner, and the general approach and classification are helpful. The clinical features of the various manifestations are well set out; these and the histopathology are both well illustrated.

The early chapters on the biochemistry and the metabolism of fats is a clear introduction to the humoral and intracellular disturbances which accompany the varied manifestations of these related disorders. In addition to the major chapters dealing with the xanthomatoses associated with diabetes, glycogen storage disease, nephrotic syndrome, pancreatitis, etc., there are valuable sections on the rarer diseases showing lipoid disturbances. Gaucher's disease, naevoxanthoendothelioma, and the diseases grouped under histiocytosis X and others are well presented and discussed.

This is a useful work of reference, and is well written and presented in every way. The only bad feature is the name, which is ugly and adds nothing useful to the subject.

J. T. INGRAM.

ESSAYS FROM JUNG

The Structure and Dynamics of the Psyche. By C. G. Jung. Translated by R. F. C. Hull. (Pp. 596; illustrated. 42s.) London: Routledge and Kegan Paul. 1960.

Students of psychiatry, knowing something of Jung's standpoint, will do well to read this book, for the eighteen essays, written by Jung, give the best available survey of his work. A start should be made with the chapter entitled "On the Nature of the Psyche," and then Chapter 1, "On Psychic Energy," containing Jung's comprehensive answer to criticisms of his libido theory, touched on several years earlier in *Symbols of Transformation.* Dreams with their peculiar structure and origin occupy a central place in the therapy of analytical psychology, and the chapter on "General Aspects of Dream Psychology" is clear and informative. Two of the sections—"Basic Postulates of Analytical Psychology" and "The Stages of Life"—will be familiar to those who have read *Modern Man in Search of a Soul.*

Coming to terms with the unconscious is discussed explicitly in "The Transcendent Principle," now published for the first time. It also contains an account of "active imagination," a clinical procedure derived originally from Freud's free-association technique, although bearing little resemblance to it. Analysts employ the method on selected cases, and often it takes visible shape by painting and modelling.

Jung's tentative conclusions on the obscure problems relating to synchronicity are given in the final chapter, "Synchronicity: an Acausal Connecting Principle." We may find it difficult to imagine events that are connected non-causally and are capable of non-causal explanation. Yet their existence is at least a possibility. Our scientific picture of the world has been altered by the discoveries of modern physics; and natural laws, being statistical truths dependent on the principle of causality, no longer possess absolute but only relative validity. When meaningful coincidences occur, the principle of causality as a basis of explanation proves inadequate. Each of us could at once give examples of such events. But the explanation "Merely a coincidence" is not acceptable. To Jung these occurrences suggest the possibility of some as yet unrecognized principle operative in everyday life. Hence his interest in the matter.

Hull's translation is admirable.

E. A. BENNET.

RADIOLOGY OF BONES

Principles of Bone X-ray Diagnosis. By George Simon, M.D., M.R.C.P., F.F.R. (Pp. 170+8+xxi; illustrated. 57s. 6d.) London: Butterworth and Co. (Publishers) Ltd. 1960.

Following the success of his book, *Principles of Chest X-ray Diagnosis,* Dr. Simon has now done a similar one on *Principles of Bone X-ray Diagnosis.* This is a useful book, though probably the radiology of bones does not lend itself quite so easily as chest radiology to the pattern that Dr. Simon has adopted. So far as bone radiology is concerned the book would have been more valuable had it been rather longer, as certain aspects of bone work could have been covered more fully with advantage and the whole could have been more complete.

The production is up to Butterworth's usual high standard, and, allowing for the limitations above mentioned, it should be a useful book to include in a radiological library.

J. W. MCLAREN.

BIOLOGICAL TECHNIQUES

Tools of Biological Research. Edited by Hedley J. B. Atkins, D.M., M.Ch., F.R.C.S.Eng., Hon.F.A.C.S. With an Introduction by Lord Cohen of Birkenhead. (Pp. 175-xii; 37s. 6d.) Oxford: Blackwell Scientific Publications. 1960.

This book contains short reviews on electron spin resonance spectroscopy, paper chromatography, the ultracentrifuge, *x*-ray studies in biological research (*x*-ray crystallography), fluorescent antibody techniques, the cathode ray oscillograph and its application to electromyography, and microradiography.

It should be valuable to clinicians who require brief and readable accounts of these subjects, while research workers who are embarking on a project which involves the use of one of these techniques will find the relevant chapter useful introductory reading and a source of references. The physical principles are described and examples of the application of these methods in the biological and medical fields are given. The publication of this book is encouraging evidence of the increasing participation of workers trained in diverse scientific disciplines in the investigation of clinical problems.

R. W. E. WATTS.

RADIOACTIVE ISOTOPES IN BIOCHEMISTRY

Radioactive Isotopes in Biochemistry. By Engelbert Broda. With a Preface by G. de Hevesy. (Pp. 376+x; illustrated. 57s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. 1960.

The use of isotopically labelled materials in biochemical investigations is extending so rapidly that a new work on the application of radioactive isotopes in this field is most welcome, particularly when it is as authoritative and detailed as Dr. Broda's book.

First published in 1958, and now appearing in an excellent English translation, this is a review of the radioactive tracer techniques available for the study of fundamental biochemical mechanisms. Although the author claims only to describe and illustrate the methods involved, his survey of results is extensive, involving references to about 3,000 authors and nearly 4,000 papers. The concentration on radioactive tracers might seem artificial when the uses of stable isotopes overlap so much in scope, but the results with stable labelling are commonly referred to, and the intention to describe techniques and their application makes this limitation to radioactive methods both reasonable and desirable in a subject of this extent.

Dr. Broda makes the introductory statement that he is dealing primarily with biochemistry and molecular events, rather than physiology and visible functioning of organs; and that "in this book some consideration of physiology is inevitable, but specifically medical questions will be avoided as far as possible." This is fair enough for such an extensive survey of fundamental biochemical studies as he has produced, though it may be felt that the metabolism of, for example, thymidine or thyroxine merited more than the passing mention that they receive here. The fullest detail is given on the major problems of intermediary metabolism and on methods of radiochemical synthesis and determination, with brief sections on chromatographic, column, and electrophoretic separation methods, on radiation protection problems, and on the metabolism of elements. Recent manuals of radioisotope applications show a welcome tendency to deal exhaustively with special fields of application of these materials, and Dr. Broda's work is of the greatest value in this way.

E. E. POCHIN.

CLINICAL APPLICATIONS OF PATHOLOGY

Essential Principles of Pathology. By John W. Landells, M.A., M.B., M.R.C.P., F.Z.S. (Pp. 278+ix; illustrated. 25s.) London: Pitman Medical Publishing Co. Ltd. 1959.

"This book is designed primarily for the medical student at the start of his clinical course" at a time when he is not prepared "to assimilate a great mass of detailed or theoretical knowledge about diseases which are as yet merely names to him." So runs the first sentence in the author's introductory chapter, and in the foreword Dr. A. E. Clark-Kennedy tells us that Dr. Landells's book "will give the beginner that essential knowledge of the subject that he must gain as quickly as possible when starting clinical medicine."

The title of the book is rather misleading. There is certainly a commendably simple introductory outline of the scope and general principles of pathology, but throughout the book the author grasps every opportunity to bring his subject to life by frequent reference to a common disease, a clinical picture, or a clinical sign. In other words, he does his utmost to inculcate the habit of clinicopathological correlation, and for this reason alone his little book will be of material help to the student during the first six months of his clinical apprenticeship and is very likely to convince him that the study of pathological anatomy and histology is an integral part of his clinical training rather than a separate scientific discipline which will eventually terminate in yet another examination.

The ground covered by this book of only 270 pages is surprisingly extensive. This has been achieved by the use of a clear, direct, and attractive style and by sacrificing detailed description to convincing explanation. Dr. Landells has written a sound guide to the application of pathology to clinical medicine. His book could be read through without much effort in four or five evenings, it can be easily carried in a coat pocket, and the price is exceptionally modest. A companion volume introducing the junior clinical student to bacteriology is about to be published.

G. HADFIELD.

UROLOGY IN THE FEMALE

Gynecological Urology. Compiled and edited by Abdel Fattah Youssef, M.B., D.S., D.G.O., M.Ch., F.I.C.S. Foreword by Naguib Mahfouz, M.Ch., F.R.C.S.(Hon.), F.R.C.P., F.R.C.O.G.(Hon.) (Pp. 893+xvii; illustrated. £9.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1960.

This compendium of knowledge concerning the development, anatomy, function, and diseases of the female urinary apparatus is supplied by 32 well-known authorities drawn from Egypt, Austria, Germany, Scandinavia, U.S.A., and Great Britain. By concentrating on getting contributions by "big names" rather than on the overall plan, the editor has involved himself in the problem of overlapping material. Is it really wise to have nine different authors writing separate chapters on urinary fistulae, excellent though these all be individually? This arrangement, as well as clashes and repetitions on the subjects of urinary retention, urethral incontinence, and of the methods for investigating the urinary tract, help to make the book bulky. However, the text is not so extensive as at first appears because a large attractive type is used and there are many illustrations of high quality.

The outstanding sections of this intriguing if costly book are undoubtedly those concerned with surgical technique. Operations for fistulae, ureteric injuries, stress incontinence, anterior exenteration, cystectomy, and the creation of an artificial bladder are described clearly and with authority. But anyone looking for information on certain basic matters concerned with pathology, and with the nature and causes of dysfunctions of the bladder and urethra, has to be content with brief accounts of orthodox or unorthodox views which are not always in accordance with modern knowledge. And, while certain interesting subjects such as urethral prolapse escape mention, unnecessary attention is given to unimportant and nebulous conditions such as "menouria" and "endocrine cystopathies."

It is very difficult to assess this work as a whole, and perhaps this reflects its main weakness. It is not a whole but a series of essays of varying quality; some are very good, some not so good. The discerning reader will select accordingly.

T. N. A. JEFFCOATE.

SYMPOSIUM ON UVEITIS

Documenta Ophthalmologica. Advances in Ophthalmology. Volume XIV. Edited by G. von Bahr, G. B. Bietti, J. ten Doesschate, H. Fischer-von-Bünau, J. François, H. Goldmann, H. K. Müller, Jean Nordmann, A. J. Schaeffer, Arnold Sorsby. (Pp. 413; illustrated. 72 guilders.) The Hague: Uitgeverij Dr. W. Junk. 1960.

This volume is devoted to a symposium on uveitis held in Munich in September, 1959, and consists of a series of papers and discussions under the chairmanship of

Professor Marc Amsler. The papers can be divided into two main groups: clinical descriptions of some types of uveitis, and pathological and serological investigations on aqueous humour and serum from cases of uveitis.

Under the title, "Dyscrasic Uveitis," Appelmans and Michiels discuss the clinical features of allergic uveitis, post-traumatic uveitis, and uveitis associated with endocrine disorders, the collagen diseases, and some haematological conditions. The clinical features of Behçet's disease are described by Bouzas, and Sezer reports his virological findings, though adding little to his previously published work.

The role of tuberculosis in uveitis is discussed in papers by Rohrschneider, Bouzas, Cross, and Remky, and it is interesting to note that the aetiological importance of tuberculosis in this condition is declining. Focal infection is still incriminated by Offret and Saraux in 25 to 50% of cases; though Coles was unable to find any correlation between anti-streptolysin-O titres in the blood and either anterior or posterior uveitis suggesting that the streptococcus was not an aetiological factor. The aetiological studies of Oksala demonstrate that electrophoretic patterns are frequently abnormal in uveitis, supporting the view that it is part of a systemic disease.

The clinical features and diagnosis of toxoplasmosis are discussed by Straub and by Weekers and his colleagues. Straub notes the particular frequency of juxtapapillary choroiditis and suggests that comparison of antibody in aqueous and serum is a promising diagnostic method. Jacobs reports experimental work suggesting that some strains of Toxoplasma show persistent activity with late parasitaemias which may account for the appearance of uveitis in patients with no clinical evidence of acute infection. The problem of late relapses is discussed by Amalric and Bessou. Remky, using the comparative dye test titres in aqueous and serum, finds that 20% of cases with posterior uveitis are toxoplasmic and emphasizes the importance of this test in diagnosis.

The role of leptospirosis (Witmer and Moro), brucellosis (Witmer), the rickettsiae (Thomas and his colleagues), and viruses (Bietti) in the causation of uveitis are also discussed.

Investigations on the aqueous humour were concerned with the demonstration of antibodies (Remky, Bozsóky and Laffers), bacteriological and microscopical examination (Bouzas and Agarwal), and micro-electrophoresis (François and Rabaey). The use of fluorimetry to detect reactions resulting from the injection of antigens is described by Lugossy. The principles and indications for treatment with corticosteroids and chemotherapeutic agents are described by Kless.

From the wealth of detailed information in these papers and the discussions it is difficult to draw general conclusions. The main value of symposia such as these is the intellectual stimulus to the participants, and the publication of the proceedings is bound to leave the reader who has not participated in some bewilderment at the unresolved differences of opinion. The clinician who hopes to find from this volume a solution to the many problems concerning the management of cases of uveitis will be disappointed, but to the pathologist and research worker the book will be valuable as an indication of the latest ideas on the laboratory investigation and on the immunological theories of uveitis.

E. S. PERKINS.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Ring the Night Bell. The Autobiography of a Surgeon. By Paul B. Magnuson. Edited by Finley Peter Dunne, jun. (Pp. 376 + viii. 25s.) London, Melbourne, Toronto: Heinemann. 1960.

A Synopsis of Ophthalmology. By J. L. C. Martin-Doyle, M.R.C.S.(Eng.), L.R.C.P.(Lond.), D.O.(Oxon.), with a foreword by H. B. Stallard, M.B.E., M.A., M.D.(Cantab.), F.R.C.S.(Eng.), Hon.LL.D.(St. Andrews). Second edition. (Pp. 249 + x. 27s. 6d.) Bristol: John Wright and Sons Ltd. 1961.

Klinische Statistik der Diebetsichen Nephropathie. By Professor Dr. med. Habil. Georg Heuchel. (Pp. 112 + vii. DM. 15.) Jena: Veb Gustav Fischer Verlag. 1961.

Intra-abdominal Crises. By Kenneth D. Keele, M.D., F.R.C.P., and Norman M. Matheson, F.R.C.S., M.R.C.P., F.A.C.S. (Pp. 397 + xii; illustrated. 50s.) London: Butterworths. 1961.

Northern Rhodesia in the Days of the Charter. A Medical and Social Study, 1878, 1924. By Michael Gelfand, C.B.E., M.D., F.R.C.P. (Pp. 291 + xiii. 30s.) Oxford: Basil Blackwell. 1961.

X-Ray Microscopy and X-Ray Microanalysis. Proceedings of the Second International Symposium (Stockholm, 1960). Edited by A. Engström, V. Cosslett, H. Pattee. (Pp. 542 + x; illustrated. £5.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. 1960.

Toxicology and Biochemistry of Aromatic Hydrocarbons. By Horace W. Gerarde, M.D., Ph.D. (Pp. 329 + xiii; illustrated. 30s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Company. 1960.

The Birth of a New Physics. By I. Bernard Cohen. (Pp. 200; illustrated. 5s.) London, Melbourne, Toronto: Heinemann. 1960.

Waves and the Ear. By Willem A. Van Bargeijk, John R. Pierce, and Edward E. David, jun. (Pp. 235; illustrated. 5s.) London, Melbourne, Toronto: Heinemann. 1961.

The Physics of Television. By Donald G. Fink and David M. Lutyens. (Pp. 160; illustrated. 5s.) London, Melbourne, Toronto: Heinemann. 1961.

Crystals and Crystal Growing. By Alan Holden and Phylis Singer. (Pp. 320; illustrated. 10s. 6d.) London, Melbourne, Toronto: Heinemann. 1961.

Belfast and Its Charitable Society. A Story of Urban Social Development. By R. W. M. Strain. (Pp. 333 + xvi; illustrated. 45s.) London, New York, Toronto: Oxford University Press. 1961.

Transactions of the Ophthalmological Society of the United Kingdom. Volume LXXX. Session 1960. (Pp. 708 + lxxi; illustrated. No price.) London: J. and A. Churchill, Ltd. 1961.

L'Enfisema Polmonare Fisiopatologia, Clinica e Terapia. By Emilio Sartorelli, Max Magistretti, and Antonio Grieco. (Pp. 184 + v. L. 4,000.) Milan: Edizioni Minerva Medica. 1960.

Understanding Interrelations in Nursing. By Lester D. Crow, Ph.D., and Alice Crow, Ph.D. (Pp. 461 + xiii; illustrated. No price.) New York: The Macmillan Company. 1961.

A Synopsis of Contemporary Psychiatry. By George A. Ulett, B.A., M.S., Ph.D., M.D., and D. Wells Goodrich, M.D. Second edition. (Pp. 309. 48s. 6d.) London: Henry Kimpton. St. Louis: C. V. Mosby Company. 1960.

Culture Methods for Invertebrate Animals. A Compendium prepared co-operatively by American zoologists under the direction of a committee from Section F of the American Association for the Advancement of Science. By Paul S. Galtsoff, Frank E. Lutz, Paul S. Welch, James G. Needham (Chairman). (Pp. 590 + xxxii + 15. $2.75.) New York: Dover Publications Inc. 1960.

Island of Terrible Friends. By Bill Strutton. (Pp. 192. 15s.) London: Hodder and Stoughton. 1961.

Frau und Sport. Ein Leitfaden für Ärzte, Sportlehrer, Krankengymnastinnen und Sportlerinnen. By Professor Dr. E. J. Klaus and Professor Dr. H. Noack. (Pp 156 + viii; illustrated. DM. 19.80.) Stuttgart: Georg Thieme Verlag. 1961.

Die Thromboembolischen Erkrankungen. Edited by Professor Dr. Th. Naegeli, Doz. Dr. P. Matis, Professor Dr. R. Gross, Professor Dr. H. Runge, and Professor Dr. H. Sachs. (Pp. 1,045 + viii; illustrated. DM. 158.) Stuttgart: Friedrich-Karl Schattauer Verlag. 1961.

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ANTICOAGULANT THERAPY IN CEREBROVASCULAR DISEASE

Doubt increases rather than diminishes on the best way to manage patients with cerebrovascular disease. Before the development of sympathetic block, arterial clearance, and anticoagulant therapy, management remained quietly expectant, for no positive decision was called for until the stage of rehabilitation was reached. All has now changed dramatically, particularly in relation to anticoagulant therapy. Early reports from the United States, including those of C. M. Fisher[1] and C. H. Millikan and colleagues,[2 3] suggested that anticoagulants produced striking benefit in reducing attacks of cerebral ischaemia and diminishing the fatality rate, though R. Schäfer[4] was unconvinced of this. Apart from considerations of expense, the main obstacle to the widespread use of anticoagulants in cerebrovascular disease is the fear of causing haemorrhage, and the present hesitancy over therapy is an uneasy compound of certainty about the dangers of anticoagulants and doubt about their efficacy.

The danger of producing haemorrhage into the infarcted heart by the administration of anticoagulants to patients with coronary disease seems not to have been investigated; in this type of case iatrogenic haemorrhage has been principally into the skin and mucous membranes. It is interesting to note that only one case of cerebral haemorrhage was recorded in the large series of patients treated under the Medical Research Council trial of anticoagulants in coronary disease.[5] On the other hand, Sir Russell Brain[6] and Sir Charles Symonds[7] have drawn attention to the possibility that an ischaemic brain infarct might become haemorrhagic under the influence of anticoagulants. Experimental work by M. W. Wood and colleagues[8] seems to show that this is a real danger, and W. A. Sibley and colleagues[9] were also led to this conclusion.

In the face of such evidence the evaluation of the results of anticoagulant treatment calls for careful clinical observation combined with precise diagnosis of the cerebrovascular disturbance. Clearly the slightest suspicion that the cerebral disorder is haemorrhagic constitutes an absolute contraindication to anticoagulants. The controlled trial carried out by A. Bradford Hill and colleagues[10] ended "earlier than had been anticipated" as a result of fatal haemorrhages in five patients receiving anticoagulants. The control cases had no such haemorrhages. As Bradford Hill and his associates point out, these haemorrhagic fatalities could conceivably have been due to errors in the presumptive initial diagnosis of thrombosis, so that the administration of anticoagulants may have increased an existing relatively small haemorrhage. Yet the fact that the incidence of other, non-fatal, vascular disorders was no greater in the control group than in the treated group suggests that there is no clear clinical advantage to be set against this risk of presumed misdiagnosis.

These doubts about the effectiveness of long-term anticoagulant treatment in cerebrovascular disease are echoed by those of J. McMichael and E. H. O. Parry[11] in relation to myocardial infarction, and constitute a cogent argument against the uncritical application of a method of treatment which is troublesome to the patient, arduous to the doctor, and expensive to the community. Are there, then, sound indications for the administration of anticoagulants in these cases? Millikan and colleagues[3] advise giving them for six months in cases of intermittent insufficiency in the carotico-vertebral systems, in vertebro-basilar thrombosis, and in advancing carotid occlusion. A. B. Carter[12] is also impressed with the value of a four-week course of treatment in cases of incomplete cerebral infarction of slow onset. Further, E. McDevitt and colleagues[13] conclude that the frequency of thrombo-embolic attacks in heart disease is significantly reduced. *A priori* there is something to be said for these views, despite the hazard of fatal haemorrhage, though it must be admitted that the Millikan series[3] did not include statistically acceptable controls and the work of Carter[12] was concerned only with short-term effects. It certainly seems that anticoagulant therapy is not considered suitable for cases of complete thrombosis. But there does now seem to be a need for a controlled trial of the long-term administration of anticoagulants in carefully selected cases belonging to the groups specified by Millikan, for it is in those cases that the most benefit may be achieved with the least risk.

1 Fisher, C. M., *Neurology (Minneap.)*, 1958, **8**, 311.
2 Millikan, C. H., Siekert, R. G., and Schick, R. M., *Proc. Mayo Clin.*, 1955, **30**, 116.
3 ——— and Whisnant, J. P., *J. Amer. med. Ass.*, 1958, **166**, 587.
4 Schäfer, R., *Schweiz. med. Wschr.*, 1959, **89**, 236.
5 Medical Research Council Report, *Brit. med. J.*, 1959, **1**, 803.
6 Brain, W. R., *Lancet*, 1954, **2**, 831.
7 Symonds, C., *Practitioner*, 1956, **176**, 130.
8 Wood, M. W., Wakim, K. G., Sayre, G. P., Millikan, C. H., and Whisnant, J. P., *A.M.A. Arch. Neurol. Psychiat.*, 1958, **79**, 390.
9 Sibley, W. A., Morledge, J. H., and Lapham, L. W., *Amer. J. med. Sci.*, 1957, **234**, 663.
10 Hill, A. B., Marshall, J., and Shaw, D. A., *Quart. J. Med.*, 1960, **29**, 597.
11 McMichael, J., and Parry, E. H. O., *Lancet*, 1960, **2**, 991.
12 Carter, A. B., *Quart. J. Med.*, 1960, **29**, 611.
13 McDevitt, E., Carter, S. A., Gatje, B. W., Foley, W. T., and Wright, I. S., *J. Amer. med. Ass.*, 1958, **166**, 592.

TENDON TRANSPLANTS

The idea of substituting the tendon of a healthy muscle for one which had become paralysed was conceived first by K. Nicoladoni[1] in 1880. The early attempts at tendon transplantation often failed because of practical difficulties which have now been largely overcome. Refinements in the technique of tendon suture and the adoption, where possible, of the method of inserting the transposed tendon into subperiosteal bone have solved the problems of fixation, while the practice of passing the tendon through lax subcutaneous tissues has reduced the formation of peritendinous adhesions. With such matters of craftsmanship mastered, it became possible to assess the inherent advantages and limitations of the method and to lay down certain general rules for success. Thus the transposed muscle must be sufficiently powerful to perform the action expected of it: it must be remembered that it will lose about one-third of its power as the result of its transposition. Its nerve and blood supply must remain intact, its place of insertion should be as close as possible to that of the paralysed muscle, and its "line of pull" must be direct. Normal physiological tension must be established, and this may require additional bone-blocking procedures to limit the range of movement of a joint and prevent over-stretching. Re-education of the muscle in its new function is facilitated if it is normally synergistic with the paralysed muscle.

Paralytic poliomyelitis provided surgeons during the first half of this century with ample opportunities for applying the principles of tendon transplantation. Its usefulness was extended to include the remedy of a positive dynamic imbalance by the redistribution of the unparalysed remnant of musculature in an extensively paralysed limb. The aim is not primarily the restoration of lost functional capacity, for this ideal is often unattainable—particularly in the lower limb, in which the total remaining muscle mass may be inadequate for the task—but rather the "balancing" of surviving muscle power to eliminate progressive deformity in a growing limb. C. W. Peabody,[2] in his review of the subject in 1938, distinguished between a deformity which is "dynamic" in origin and in the growing child will recur even after bony fusion if the muscle imbalance persists, and "static" deformities which result from inability of weakened muscles, albeit adequately balanced, to withstand the deforming forces of gravity. Deformity of the latter type is not progressive, is common both to the adult and the growing child, and can be controlled by instrumentation, arthrodesis, or bone-blocking operations.

With the decline of poliomyelitis the field of usefulness of tendon transference has altered. In an appraisal of the method at a recent meeting of the British Orthopaedic Association, J. M. P. Clark[3] pointed out that flaccid paralysis from other causes is increasing. Traction injuries to the brachial plexus have become commoner with the increase in accidents to vehicles travelling at high speed, and the successful neonatal repair of spina bifida—an operation which has preserved the life of infants who in the past would have died—has made treatment for their paralyses possible. Tendon transfers also have a limited usefulness in the treatment of cerebral palsies and disseminated sclerosis.

Of the numerous muscle and tendon transplants attempted in the past a few have proved sufficiently reliable to warrant their continued use in the surgery of paralysis. No satisfactory procedure has yet been devised for the paralysed shoulder, but for the grave disability of loss of active flexion at the elbow the operation of advancement of the origins of the flexors and extensors of the fingers up the shaft of the humerus is of value, particularly when some action remains in the biceps and brachialis muscles. J. M. P. Clark's[4] procedure of transplanting the lower part of the pectoralis major into the biceps brachii tendon is valuable when weakness of the forearm muscles precludes the former operation. It is in the treatment of isolated paralysis of the hand that tendon transference is most rewarding, for here even modest gains in function are important. The classical transfer of the wrist flexors to the finger extensors in radial nerve palsy, and the use of a tendon of the flexor digitorum sublimis or palmaris longus to restore the lost power of opposition in the thumb, are both well-established procedures. Recently P. Brand[5] has described a method in which free tendon grafts are used, with the extensor carpi radialis as the motor, to simulate the action of the short muscles of the hand in ulnar nerve palsy. The results have been excellent.

In the lower limb, tendon transfers have their greatest usefulness in the control of paralytic deformities of the foot and in the relapsed club-foot. The rearrangement of such muscles as have survived requires nice judgment to avoid the hazards of over-correction, secondary deformity, and instability. Attempts to restore the lost function of extension at the knee have proved disappointing, but

[1] Nicoladoni, K., *Wien. med. Wschr.*, 1880, **30**, 1413.
[2] Peabody, C. W., *J. Bone Jt Surg.*, 1938, **20**, 193.
[3] Clark, J. M. P., ibid., 1961, **43-B**, 172.
[4] —— *Brit. J. Surg.*, 1946, **34**, 180.
[5] Brand, P., *J. Bone Jt Surg.*, 1959, **41-B**, 208.
[6] Eggers, G. W. N., ibid., 1952, **34-A**, 827.
[7] Mustard, W. T., ibid., 1952, **34-A**, 647.

the operation of inserting the hamstrings into the femoral condyles to relieve flexion deformity of the knees and hips in spastic diplegia is of value.[6] Numerous transplants have been devised for weakness of the muscles about the hip-joint, but successful replacement of the stabilizing power of the hip abductors has rarely been accomplished. The iliopsoas transfer first described by W. T. Mustard[7] succeeds in carefully chosen cases and has been used recently, in a modified form, to replace a weak gluteus maximus.

BARRIER CREAMS

Despite the volumes of contentious publicity that it receives and the large sums paid out in compensation, "industrial dermatitis" affects only a small proportion of workers. Nor is it a distinct clinical entity to be clearly differentiated from "non-industrial dermatitis." It is reasonable to regard dermatitis as being partly constitutional and partly exogenic, and to note that individuals vary greatly in their reactions to the environment.

The difficulties of precise clinical diagnosis, and of the collection and analysis of accurate data in factories, present serious problems. Eczema of the hands is known to be common, but aetiologically and therapeutically it often sets a puzzle for both general practitioners and dermatologists. Most surveys of occupational skin diseases are selective, the selection depending on such factors as referral to a dermatologist, or a particular period off work, or medico-legal aspects. Detailed surveys by a team including an experienced dermatologist and an industrial medical officer of all persons affected by cutaneous disease in an industrial community are virtually non-existent. Consequently, it is apt to be too readily assumed that an eczematous dermatitis of the hands or exposed parts in a person working with "dust, liquid, or vapour" is of occupational origin. Yet most analyses of skin disease in industry reveal a large number of cases unrelated to conditions of work, including "non-occupational dermatitis." A. F. J. Hall[1] found 36.2% of 755 cases among aircraft workers to be non-occupational; V. Pirila[2] found 47 cases among 211 cement workers; and C. C. Molloy[3] found 83 among 150 cases of dermatoses at an ordnance factory. Perhaps because of the understandable risks of adverse publicity and medico-legal complications, industrial firms usually do not encourage the publication of their data on dermatoses. But it is in the factory itself that the problems must be studied.

It is against this unsatisfactory background that the medical man tries to assess the value of prophylactic measures, and particularly of barrier creams. The term barrier cream is usually understood to mean a preparation which will prevent chemical substances from penetrating and harming the skin deep to the horny layer. It is also used, however, to designate compounds applied to the skin before dirty manual work, which will facilitate cleansing of the skin subsequently. Much experience shows that such creams are useful, but most of the experimental evidence reveals their imperfections. F. Ray Bettley[4] has recently stressed two points: first, the lack of experimental or other evidence to support the claim that such creams form an effective barrier; and, secondly, the secrecy of their composition. Care must be taken not to read more into the claims of barrier-cream manufacturers than is actually said. The manufacturers do not claim that their product prevents any molecule penetrating through the stratum corneum; and such a failure can readily be proved with contact allergens in a specifically sensitive subject. None the less, it is possible that barrier creams may have some effect in reducing the amount of irritant or sensitizing compounds with which the skin comes in contact, though there is little reliable evidence on this.

Barrier creams have been a controversial matter almost since their introduction. On one side is the obvious appeal of the theoretical concept of an invisible, almost monomolecular barrier film, and the wish (as well as the duty) of an employer to provide his workers with all that is necessary to prevent dermatitis. On the other side is a series of experiments showing the imperfections of these preparations. It is unfortunate that they have played such a large part in the medico-legal aspects of industrial dermatitis, so much so that they are sometimes denigrated as "legal creams," the implication being that they are supplied principally to protect an employer against a charge of negligence. It may seem surprising to many doctors and lawyers that an employer may be found guilty of negligence if he fails to supply a barrier cream when little or no evidence is given on the composition or efficacy of the preparation which he should have provided. In the past doctors have felt reluctant to state in court that a man would have developed dermatitis in spite of the use of barrier cream, or an "anti-dermatitis" cream, even though it is their personal opinion. This doctor's dilemma was put in a recent case by Bettley[5] to Mr. Justice Davies, who

[1] Hall, A. F. J., *J. Amer. med. Ass.*, 1944, **125**, 179.
[2] Pirila, V., *Acta derm.-venereol. (Stockh.)*, 1954, **34**, 136.
[3] Molloy, C. C., *Trans. Ass. industr. med. Offrs*, **8**, 54.
[4] Bettley, F. R., *Brit. med. J.*, 1960, **2**, 1467.
[5] *The Times*, January 17, 1961.
[6] Collier, E., *Brit. med. J.*, 1960, **2**, 1667.
[7] Cooke, M. A., and Launchbury, A. P., ibid., 1961, **1**, 292.

appreciated its significance, though it was not the most important part of the evidence on which he decided the particular case before him. In an earlier case[6] an employer won a similar action, which was taken to the House of Lords, on the ground that his medical officer advised him that the use of a barrier cream was not necessary for the prevention of dermatitis among the employees. Bettley is not alone in his opinion that barrier creams may sometimes do harm, but the general acceptance of this view waits on further supporting evidence.

If improvements in present barrier creams are to be made, they are most likely to come from a closer co-operation between the manufacturers, dermatologists, and industrial medical officers. New preparations are under trial,[7] and deserve careful study, as do all the other unsatisfactory aspects of "industrial dermatitis" at the same time. But it is worth bearing in mind that barrier creams are only a part—and some authorities would say only a small part—of the defensive measures to be taken against dermatitis. Good protection entails attention to engineering techniques so that they may help to provide a clean environment, attention to temperature control, to protective clothing, and to many other features of industrial life on which the experience of a works medical officer can be invaluable. Moreover, good morale is a helpful, perhaps essential, part of keeping healthy at work.

SEROLOGICAL REACTIONS IN RHEUMATOID ARTHRITIS

The Rose–Waaler test and its numerous modifications—the latex fixation test, the bentonite flocculation test, and so on—are due to a specific macroglobulin in the serum of most patients with rheumatoid arthritis (and some other persons). Most workers would now agree with L. E. Glynn and E. J. Holborow[1] that it is of antibody-like nature specifically directed against antigenic groups shared by many species of globulin, and, as a corollary, that "the rheumatoid subject is apparently capable of recognizing and therefore regarding as foreign a degree of change in an autogenous protein that is ignored by the immunological mechanism of normal individuals." However, some patients with rheumatoid arthritis as defined by strict clinical criteria[2] fail to give a positive titre in these tests; indeed, there is a high incidence of, apparently, rheumatoid arthritis in patients with congenital agammaglobulinaemia.[3]

The careful study recently published by A. St. J. Dixon[4] of 63 Manchester patients with initially negative Rose–Waaler tests is therefore of particular interest. These in-patients, meeting all the criteria mentioned above, were chosen because of their sero-negative reaction from a much larger number of rheumatoid patients, and reviewed again after an average follow-up period of 5.4 years. During this period other factors were discovered which led to eleven of them being classified under another heading (four cases of psoriatic arthropathy, two of reticulohistiocytosis, and one each with gout, Takayushu's syndrome, Reiter's disease, generalized osteoarthritis, and myelomatosis.) In all these patients the Rose–Waaler test had remained negative. Of 45 of these patients who still met the criteria for rheumatoid arthritis, the Rose–Waaler test became positive (1 : 32) in 10: the remainder showed negative titres (1 : 16 or less) and most of them (25 out of 35) showed clinically "typical" disease with symmetrical peripheral polyarthritis. Though several authors have commented on the rather worse prognosis of people with sero-positive rheumatoid arthritis, among those here classified as rheumatoid arthritis at follow-up the only three fatalities were in the still sero-negative subgroup. Perhaps given more time they might have "converted," since this process may take up to twenty-three years. It is difficult to comprehend the entire picture without a similar analysis of those other hundreds of patients with sero-positive disease or in the no-man's-land of intermediate titres, but this is a notable analysis of an important section of the total rheumatoid population of the British Isles, which has been estimated at nearly two million.

The main conclusion we may draw is that the sheep-cell agglutination test is valuable in research, while a negative result should alert us to possible diagnostic error; but for the individual patient it is not, in its present form and in our present state of knowledge, a reliable guide to prognosis or treatment. However, rheumatoid arthritis, though recognized in patients showing a positive Rose–Waaler test[5] not treated with steroids, does seem to have increased recently, particularly in the more severely ill patients, almost invariably treated with steroid. Perhaps in view of the decrease in Rose–Waaler titre on gold treatment[6] and its increase on prednisone treatment,[7] the test may have some implications for therapy.

EXPLOSION OF ANAESTHETIC GASES FROM THE STOMACH

So long as flammable anaesthetics continue to be used, the risk of fire and explosion must be considered however small it may be made. In Great Britain we have gone a long way in putting into operation almost every known precaution to prevent this occurrence. A question, however, which commonly arises, and which cuts across these precautions, is how to estimate the interval which should elapse between the withdrawal of a flammable anaesthetic and the safe use of diathermy or the cautery.

[1] Glynn, L. E. and Holborow, E. J., *Ann. rheum. Dis.*, 1960, **19**, 197.
[2] Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. A., *Bull. rheum. Dis.*, 1956, **7**, 121.
[3] Gitlin, D., Janeway, C. A., Apt, L., and Craig, J. M., in *Cellular and Humoral Aspects of the Hypersensitive States: A Symposium held at the New York Academy of Medicine* (Section on Microbiology, Symposium No. 9), ed. H. S. Lawrence, p. 425. New York and London. 1959.
[4] Dixon, A. St. J., *Ann. rheum. Dis.*, 1960, **19**, 209.
[5] Bywaters, E. G. L., ibid., 1957, **16**, 84.
[6] Empire Rheumatism Council Research Subcommittee Report, ibid., 1960, **19**, 95.
[7] Medical Research Council/Nuffield Foundation Joint Committee Report, ibid., 1959, **18**, 173.

There is much evidence that, once the administration of, say, ether is stopped, the time during which the expired air is flammable is a matter of some minutes. It seems that after 15–20 minutes an explosion of expired vapour from the lungs is extremely unlikely to occur. B. L. de Nava and T. F. McDermott[1] have now drawn attention to the stomach as a reservoir of flammable anaesthetic vapours as distinct from fermentative ones. They report a case in which an explosion occurred two and a half hours after the termination of an anaesthetic consisting of ethylene and oxygen. They proceeded to investigate the times during which various explosive anaesthetic mixtures are retained when introduced into the stomach of a dog. Their observations are startling. Mixtures of ethylene and oxygen were flammable for up to 4½ hours, nitrous oxide, oxygen, and ether for up to 50 minutes, cyclopropane and oxygen for up to 45 minutes, and oxygen and ether for up to 35 minutes. In general the higher the oxygen content the shorter was the time that a flammable mixture was retained.

It seems, therefore, that our estimate of the interval which must elapse after the end of an anaesthetic to make explosion unlikely has been too short. With certain anaesthetics it extends well into the post-operative period. Since inflation of the lungs often inflates the stomach as well, this risk is probably greater now than formerly. That explosions have in fact not been clearly due to this cause is probably explained by the rare use in Great Britain of controlled respiration during ether anaesthesia. Once again we are faced by the inescapable conclusion that the only certain way to avoid an anaesthetic explosion in the presence of ignition is to avoid an explosive anaesthetic.

ADMISSION TO HOSPITAL

At its meeting last week, reported in this week's *Supplement*, the Council heard a statement by the chairman of the Central Consultants and Specialists Committee, Mr. H. H. Langston, on the admission of patients to National Health Service hospital beds. Six weeks ago the Joint Consultants Committee also commented[2] on the subject and referred to reports that sometimes patients not in urgent need of treatment obtained priority of admission after being seen in private consultation. The Joint Committee could not say that this happened, but agreed that it should not. The management of waiting-lists was the overall responsibility of consultants, and every consultant, in the Joint Committee's view, should see to it that urgent and semi-urgent cases got their proper priority, and that patients not in urgent need of in-patient treatment, irrespective of how they were first seen, should be admitted in fair sequence. Mr. Langston told the Council that his Committee was in complete agreement with the Joint Committee.

Since the Joint Committee's statement, Dr. A. A. Dunlevy, radiologist to the South Manchester group of hospitals, writing in the *Lancet*,[3] has made specific charges that the hospital facilities are being irregularly used for private patients in his own district. These allegations were quoted in the lay press and repeated by Dr. Dunlevy in a television interview. Apparently they had been made before, and the hospital management committee concerned and the Manchester Regional Hospital Board had looked into them. Dr. E. A. Gerrard told Council that in his view the allegations were largely unfounded. Nevertheless, many doctors are concerned about these accusations and about the manner in which publicity has been given to them, and they will be glad to know that the Manchester Regional Consultants and Specialists Committee is meeting next week to inquire into the matter.

[1] de Nava, B. L., and McDermott, T. F., *J. Amer. med. Ass.*, 1960, 174, 2023.
[2] *Brit. med. J., Supplement*, 1961, 1, 60.
[3] Dunlevy, A. A., *Lancet*, 1961, 1, 718.

THE NEW ESTIMATES

A year ago it was realized that the Health Service estimates for the new financial year (1960–1) were out of date as soon as they were published. For they made no allowance for the cost of the Royal Commission's recommendations on doctors' pay, and large supplementary estimates were accordingly expected. In the event, the final bill presented for the year just ended (though the amount actually spent may well turn out to be less) was about £57 million more than the original one. Of this extra sum required, £41 million represented increased pay for doctors (£24 million for back payments to March, 1957, and the balance a year's cost), rather more than £8 million increased pay for other staff, and £5 million and £2 million respectively for the higher cost of the pharmaceutical and dental services.

Thus, as the table shows, the taxpayer had to find an additional £48 million in the year just ended. In the new financial year (1961–2) the distortion caused by the back payments to doctors has been removed. Even so, the rise in the gross cost to almost £850 million is fairly formidable; nor does the total include the expenditure of local health authorities, which is expected to rise considerably over the next years if the Minister of Health's plans for extending the provision of community care for the mentally disordered are fully carried out. The cost of the local health services may be around £70 million a year at present; the taxpayer's contribution to this sum is now included in the general Exchequer grant to local authorities.

	Original Estimate 1960–1 (£ million)	Final Estimate 1960–1 (£ million)	Original Estimate 1961–2 (£ million)
Gross total expenditure of which:	**774**	**831**	**849**
Hospital advances:			
Capital	29	28	35
Maintenance	458	483	501
General medical services	78	101	87
Pharmaceutical service	87	92	96
Dental service	58	60	64
Ophthalmic service	17	17	18
Less:			
Patients' payments:			
Hospitals	6	6	7
Pharmaceutical service	12	13	24
Dental service	10	10	12
Ophthalmic service	6	6	7
Health service contributions	111	114	148
Superannuation contributions and other receipts	45	50	51
Net cost to taxpayer	**584**	**632**	**600**

For the time being, as was explained in the *Journal* on February 11 (p. 418), the taxpayer is to be relieved

of the obligation to meet all the increase in the cost of the Health Service. If the 1961–2 estimates[1] are compared with the original estimate for last year (in order to eliminate the distorting effect of the back payments) the gross increase is £75 million, of which something like £38 million represents higher pay for medical men and women, nurses, and other hospital staff. The drugs bill has increased by only £4 million on the final estimate for last year, though by £9 million on the original estimate, and the whole of this increase—and a bit more—is expected to be paid for by patients through the doubled prescriptions charge. The bulk of the relief for the taxpayer is, however, to be provided by the higher weekly Health Service contribution, the new rate of which comes into force in July.

ROENTGENS, RADS, REMS, AND CURIES

The familiar units with which we were brought up to measure a cricket pitch or weigh the week-end joint have been found unsuited to measuring nuclear radiations. But since the benefits and hazards of these rays came to play a prominent part in our lives, and to be frequently reported on, some knowledge of the units in which they are measured is useful. The following brief discussion of them is intended to help the uninstructed reader over the stile.

A *radioactive* element is one whose atoms are not entirely stable, and may disintegrate at any time with the emission of *radiation* of one kind or another. The *activity* of any portion of radioactive material can be specified by quoting the number of atomic disintegrations which occur within it per second. For instance, in any sample containing 1 g. of the element radium there are 3.7×10^{10} disintegrations of radium atoms per second. For historical reasons this rate of disintegration is taken as the conventional unit, and is called the *curie*. A preparation containing 27 curies of any specified radioactive element is thus a quantity of material in which $27 \times 3.7 \times 10^{10}$ atoms (about one million million atoms) of that element disintegrate per second. An activity of one micro-micro-curie ($\mu\mu$c), to take another example, corresponds to the disintegration of one atom every 27 seconds in the sample of material considered. The mass of material associated with an activity of 1 curie depends chiefly on the average lifetime of the radioactive element in question; it may amount to tons of uranium, which decays much more slowly than radium, or to micrograms for elements of short life. In every case the activity in curies is proportional to the number of disintegrations taking place per second in the piece of material considered.

The activity of a radioactive preparation is by no means the whole story, however. Different elements emit radiations of widely different kinds, some easily absorbed, others very penetrating, and it is the absorption of these radiations in cells and tissues, rather than the disintegration of the radioactive atoms themselves, which produces the biological effects. In the same way, when *x* rays are used, it is not the transmitted radiation but the radiation actually absorbed in the tissues which causes biological damage. To assess these effects quantitatively we need some physical measure of the radiation absorbed. The simplest quantity invented for this purpose is called the *absorbed dose*, and is defined as the energy deposited by the radiation per gramme of the irradiated object. This absorbed dose could be measured, for example, in calories per gramme, and to do so would indeed serve as a reminder that most of the absorbed energy is finally degraded to heat. In practice, however, a special unit has been adopted, which is of more convenient size. It is called the *rad* and is equal to 2.4×10^{-6} calories per gramme (or 100 ergs per gramme). A dose of one million rads to water would therefore raise its temperature by only 2.4° C., and yet a few hundred rads of penetrating radiation is lethal to most animals.

The biological effects produced by different types of ionizing radiation—*x* rays, neutrons, alpha particles, etc.—differ from one another quantitatively rather than qualitatively. A particular degree of chromosome damage, for example, may be caused by an absorbed dose of one rad of neutrons or by, say, 10 rads of *x* rays. In such a case the neutrons are said to have a relative biological efficiency (R.B.E.) of 10 with respect to the *x* rays. When persons are liable to be exposed to a mixture of different radiations it is convenient to have some number which will sum up the overall effect of the radiation exposure. This may be obtained by calculating from the doses of the separate radiations the "equivalent dose of *x*-radiation," using R.B.E. factors appropriate to each type of radiation. Such equivalent doses are expressed in *rems* (*r*oentgen *e*quivalent for *m*an). This method of expressing radiation dose is less rigorous than the other quantities and units referred to above, as it depends on a somewhat arbitrary choice of R.B.E. factors, but it is adequate and convenient in work on protection against radiation.

Another concept, now called *exposure dose*, has long been used to express the amount of *x*- or gamma radiation to which a person may be exposed, and the unit appropriate to this concept is called the *roentgen*. Exposure dose assesses the amount of radiation in terms of the electrical conductivity which the radiation produces (or would produce) in air. This method of specifying exposure to radiation was originally chosen because of the ease with which accurate measurements could be made, and thus reproducible exposures given. It is still very convenient for *x*- or gamma radiation, but is not applicable to other radiations. Moreover, materials of different chemical composition—for example, bone and soft tissue—exposed to the same number of roentgens will experience different *absorbed doses*. If the exposure dose is known, however, the corresponding absorbed doses in different materials can be calculated approximately, and thus exposure dose has a certain generality which makes it useful in specifying the field of radiation around a source. When soft tissue is given an *exposure dose* of 1 roentgen of *x*-radiation, the absorbed dose in the tissue is a little less than 1 rad. The magnitude of the rad was, indeed, chosen so that soft-tissue dose would have about the same numerical value whether specified in rads or roentgens.

[1] *1961/62 Civil Estimates, Class V—Health, Housing, and Local Government.* H.M.S.O., London. Price 10s. net.

BIOCHEMICAL SOCIETY'S JUBILEE

PRESENT KNOWLEDGE OF THE STRUCTURE AND SYNTHESIS OF MACROMOLECULES

The main event of the Biochemical Society's Jubilee Celebrations (see *Journal*, April 8, p. 1020) was a symposium on "The Structure and Synthesis of Macromolecules." This was held at the Senate House of London University on March 27 and 28, and was introduced by Professor F. G. YOUNG, F.R.S. The symposium was concerned with proteins, nucleic acids, and polysaccharides, and we are indebted to special correspondents for the following account of it.

The other major events were the Third Hopkins Memorial Lecture, which was given by Sir HANS KREBS, F.R.S., on "The Physiological Role of Ketone Bodies," and the Anniversary Dinner.

PROTEINS

It is almost exactly 50 years since Bateson first suggested that genes control the synthesis of enzymes. Could he have been present, he would have enjoyed listening to the three lectures by Dr. M. PERUTZ (Cambridge), Professor EMIL SMITH (Salt Lake City), and Professor J. MONOD (Paris) on protein structure and enzymes.

It is now accepted that the function of genes is to store information. This coded information can be passed from nucleus to cytoplasm and there translated into instructions for the synthesis of new proteins. The cell is, however, a closely integrated complex with efficient homoeostatic mechanisms, and any theory of gene control must explain not only the transfer of information regarding structure but also the control of reaction rates. Professor MONOD suggests that at least two types of gene exist, one type being concerned with control of protein specificity and the other with the control of reaction rates in the biosynthesis of proteins. Experiments designed to test these ideas have been performed with *Escherichia coli* and they are consistent with the assumption that the one primary product of gene action is a ribonucleic acid messenger which instructs the cell ribosomes as to which proteins should be synthesized. Control resides in the repressor genes which can repress the synthesis of messenger ribonucleic acid.

Importance of Amino-acid Sequence

Although the gene itself is still something of a mystery, proteins, the final products of gene action, are rapidly yielding their structural secrets to the newer methods of biochemistry and biophysics. In the hands of Perutz and Kendrew the technique of *x*-ray analysis has permitted the preparation of three-dimensional pictures of haemoglobin and myoglobin. The technique has much in common with the technique by which a histologist builds a composite picture of cell structure by examining serial sections of a tissue block. At the present resolution of 2 Ångstrom units, reconstruction from *x*-ray photographs of haemoglobin crystals obscures some of the fine detail, but the folding of the polypeptide chains can be followed and many of the individual amino-acids can be definitely located. The resultant picture explains at least some of the specialized characters of these molecules. The α and β chains of haemoglobin fit together as closely as the fingers of clasped hands. This close fit both within a single coiled chain and between the four coiled chains which go to form the complete molecule does much to explain the drastic effect of minor changes in amino-acid sequence which results, for example, from genetic mutation. Thus in sickle-cell anaemia a single alteration in amino-acid sequence is enough to alter the fit of the molecules and to result in severe disease.

Determination of amino-acid sequence by the now almost classical methods of Sanger and others is a process of two-dimensional analysis, but as data accumulate on more proteins it becomes obvious that the long polypeptide chains are folded in specific ways so that amino-acids which do not appear to be adjacent on a two-dimensional formulation are brought into close contact by the three-dimensional picture. It would seem that the specific three-dimensional folding is dependent on amino-acid sequence. Thus the enzyme ribonuclease can be completely unfolded by reduction and the enzymically inactive product of reduction can be reoxidized so that it recovers both its original physical properties and its original enzyme activity. It is not surprising to find, having regard to the three-dimensional structure, that the amino-acids which are especially concerned at the active centre of an enzyme may be spaced far apart in sequence on the polypeptide chain. In the proteolytic enzyme papain, out of a total of 180 residues, only 76 seem to be essential for enzyme activity. Professor EMIL SMITH and his colleagues have determined the sequence of these 76 residues. The picture which emerges does much to explain the specialized catalytic properties of the enzyme.

NUCLEIC ACIDS

The double-stranded helical structure proposed for deoxyribonucleic (D.N.A.) acid by Watson and Crick in 1953 has now been confirmed by subsequent researches. The configuration of ribonucleic acid (R.N.A.) molecules in solution, which has proved a more intractable problem, was discussed at the symposium by Professor P. DOTY (Harvard University). Model substances of high molecular weight, with the same principal structural features as ribonucleic acid itself, had provided the key to our understanding of the spatial organization of the more complex natural material, he said. These model substances, which were synthesized enzymically, had the same backbone of alternating ribose and phosphate residues found in ribonucleic acid. Whereas in ribonucleic acid there were four main purine and pyrimidine bases, in many possible sequences, polymers could be made that contained only one type of base, or two or more at the choice of the experimenter. The physical properties of these homologous polynucleotides could be studied by various techniques. These indicated that on mixing solutions of polymers with suitable bases the single ribonucleic-acid-like chains could twine around one another to form double- and even triple-stranded helices. These resembled the helix of deoxyribonucleic acid. The stability of these helices was related to the number and nature of the hydrogen bonds that formed between pairs of opposed bases, the two base pairs, similar to those postulated by Watson and Crick for deoxyribonucleic acid, giving the most stable helices. There was a strong tendency for this type of interaction to occur, and under favourable conditions the maximum possible number of base pairs formed. The order of bases in one of the polynucleotide chains might be such that the base-pairing was possible only by the buckling of the backbone so that the unwanted bases were pushed out of the helix, making a loop. The loops did not interfere with helical regions on either side. This device greatly increased the possibility of hydrogen bonding with polynucleotides having a random sequence of bases. It could occur because the backbone had a high degree of flexibility and because the chains could slide over one another until the most stable configuration was found.

Helical Organization

Methods for the detection of a helical organization had been devised and calibrated with these synthetic substances. They could be used to determine the extent of helix formation in ribonucleic acid. It had been shown that two-thirds of the ribonucleic acid chain was in the form of a helix stabilized by hydrogen-bonding between base pairs. Unlike deoxyribonucleic acid, where the hydrogen-bonding occurred between bases in two different chains that were both coiled around a common axis, the hydrogen bonds in ribonucleic

acid formed between bases in the same chain. Ribonucleic acid was supposed to be a single-stranded molecule which folded back on itself to form a number of "hairpin" regions. These were twisted to form what amounted to a double-stranded helix held in position by hydrogen bonds between opposed bases. Bases that were not opposite the complementary base were looped out. The ribonucleic acid molecule consisted of a series of such helical sections, interspersed by short lengths in which the bases were unpaired and which were more flexible.

The two strands of deoxyribonucleic acid separated when a solution was heated. The helix might be re-formed by cooling under controlled conditions with almost complete recovery of the original biochemical and physical properties. The reconstitution probably involved a preliminary interaction between a small number of adjoining bases with their partners in a complementary strand. This region then served as a nucleus for re-formation of the double helix by a co-operative or "zipping-up" process. If deoxyribonucleic acid solutions from different bacterial species were mixed and heated, re-formation of helical structure only occurred if there was a close family relationship between the species. This indicated that only when there was such a relationship was there a similarity of structure exact enough to permit exchange of the complementary strands of the helix.

The present interest in the functioning of deoxyribonucleic acid had encouraged an examination of the likelihood of interaction between the two types of nucleic acids. A double helix, of which one strand was a deoxyribonucleic-acid-like polymer and the other a ribonucleic-acid-like molecule, had been made in the laboratory. Some evidence had been obtained that deoxyribonucleic acid extracted from a cell could interact with ribonucleic acid of the same origin. Not enough was known about this phenomenon to assess its biological significance.

Biosynthesis of Nucleic Acids

Many research workers have tackled the problem of the biosynthesis of nucleic acids, because of the central role of these compounds in biochemistry. Professor J. N. DAVIDSON (Glasgow) reviewed the present state of our knowledge. He said that a system catalysing the biosynthesis of deoxyribonucleic acid could be obtained in a cell-free form. The units that were polymerized were the deoxyribonucleoside triphosphates. Pyrophosphate was split out in this reaction. A primer was required which must be a small amount of deoxyribonucleic acid that had not been extensively degraded. The amount of deoxyribonucleic acid synthesized was many times that of the added primer, and its base composition reflected accurately that of the primer. Systems of this sort had been isolated from bacterial and mammalian cells, and were most active in rapidly proliferating tissues such as bone marrow. The primer acted as a template and was faithfully copied. Deoxyribonucleic acid that had been treated so as to convert it to a single-stranded form was a more efficient primer and it was possible that on each single strand was built up its complementary chain by successive addition of nucleotide units to the end of a growing chain. The order of nucleotides in this growing chain was determined by specific base-pairing with the pre-existing chain. The rate of deoxyribonucleic acid synthesis was probably under the control of a number of feed-back systems that operated at various levels and particularly on the systems that converted ribonucleoside derivatives to the corresponding deoxyribonucleoside compounds. When a tissue started to grow rapidly a number of enzyme systems connected with deoxyribonucleic acid biosynthesis appeared in amounts larger than normal. The order in which they made their appearance corresponded to their sequence in the biosynthetic pathway.

The biosynthesis of ribonucleic acid was less well understood. An enzyme system first isolated from *Azotobacter vinelandii* caused the polymerization of the nucleoside diphosphates with the elimination of inorganic phosphate. A primer was required, but this served only as a nucleus for the addition of nucleotide units and could be as small as a dinucleoside monophosphate.

Much of the work in this field had been done by following the incorporation of radioactive precursors. This had led to the conclusion that ribonucleoside triphosphates could act as a source of ribonucleotide units in ribonucleic acid in two different ways. The first of these was the addition of nucleotide units to the ends of chains of the type of ribonucleic acid found in the cell sap which was of low molecular weight. The ribonucleoside triphosphates also provided the sub-units that were incorporated into ribonucleic acid in a random manner by systems that were found in many types of cells such as liver, thymus, chick, and pea embryo. This was a net synthesis of complete ribonucleic acid chains. The enzyme systems were located in the nucleus of the cells and required primers, of which the most effective was ribonucleic acid isolated from the nucleus. There was evidence suggesting that in some of these systems there might be a requirement for deoxyribonucleic acid. It was apparent that if the rate of progress in this and allied fields was maintained, it would soon be possible to describe the action of genes in chemical terms.

POLYSACCHARIDES

The structure and biosynthesis of polysaccharides were described by Professors E. L. HIRST (Edinburgh) and W. Z. HASSID (Berkeley). Professor HIRST emphasized that although, as the outcome of the use of modern techniques, the main structural features of many polysaccharides were known with some degree of certainty, there remained an almost infinite variety of structural detail still to be elucidated. Biological methods were now contributing to the unravelling of fine structure. Thus enzyme degradation, especially of starch and glycogen, had provided information outside the range of present chemical procedures, and agglutination reactions had been used as a means of deciding whether a polysaccharide contained two (or more) molecular species or contained a particular monomer—for example, galactose.

The various polysaccharides possessed in common well-known characters such as glycoside linkages between the sugar units and a large number of free hydroxyl groups. Their complexity was illustrated by the facts that at least 29 different sugar residues had been found and that natural polysaccharides were rarely homogenous in the sense of being substances of identical molecular weight and monomer arrangement. There might be a wide range of size with the same chemical arrangement of sugar residues, or the same pattern with differences of detail. Molecular weights might be 10^7 or more. Polysaccharides must therefore be regarded as families of closely related molecular species varying in detail. Biological specificity would be affected by such factors as the way in which the sugar units were linked, the presence of groups such as methyl or sulphate, and the degree of aggregation brought about by hydrogen-bonding between hydroxyl groups. For only a few polysaccharides were all these details known.

Mucopolysaccharides and Blood-group Polysaccharides

As examples of our present knowledge he discussed the structure of cellulose, xylan, levans, and gums and mucilages. In this context special mention might be made of the nitrogen-containing compounds of animal origin, the mucopolysaccharides and blood-group polysaccharides. They were among the most complicated molecules known, and often associated with proteins and lipids both of which had proved difficult to remove. Information gained about the few which had been intensively studied showed that the group as a whole was characterized by an essentially linear structure in which uronic acids were linked through the 1 and 4 positions to amino-sugars linked by the 1 and 3 positions, in the beta configuration and in an alternate sequence. They contained as substituent groups sulphate and N-acetyl. Thus chondroitin sulphate A was composed of equimolar amounts of N-acetyl-D-galactosamine, D-glucuronic acid, and O-sulphate. Heparin by contrast

contained alternating units of D-glucosamine and D-glucuronic acid, while hyaluronic acid had the same alternating chain as heparin but it had both N- and O-sulphate groups. A fourth type, kerato-sulphate, contained D-glucosamine and D-galactose.

The blood-group substances had as units L-fucose, hexosamine, reducing sugar, and polypeptide constituents. The group specificity was due to units made up of the sugar types, but the exact sequence which determined a particular specificity was not known. In the more complex mucopolysaccharides even the monomers were not yet fully characterized.

Biosynthesis of Polysaccharides

Professor HASSID reviewed the development in ideas about the biosynthesis of polysaccharides consequent upon the discovery by Leloir of the role of uridine diphosphate glucose as a transglycosylating agent. The formation of complex saccharides was now believed to result from transfer of the sugar moiety of such sugar nucleotides to an appropriate acceptor, thus adding monomer units by endwise apposition. The suggestion that this was a more likely mechanism than transfer from sugar phosphates was supported by the fact that the $\triangle$ F of hydrolysis of the glycoside bond of sugar nucleotides was greater than that of other possible glycosyl donors, so that this transfer reaction was the most favourable for formation of saccharide.

Sugar nucleotides were now known to be present in a number of animal and plant tissues and in bacteria. Most of those isolated contained uridine as the nucleoside, but instances of the occurrence of nucleotides containing the bases guanine, cytosine, and thymine had been reported. The impressive list of naturally occurring sugar nucleotides, moreover, now included most of the monomers found in polysaccharides.

Uridine diphosphate glucose was synthesized by animal and plant preparations from uridine triphosphate and glucose-1-phosphate by the enzyme pyrophosphorylase, the other reaction product being pyrophosphate. The reaction involved transfer of the uridyl group, which could, with an appropriate enzyme, also be transferred, for example, to galactose forming uridine diphosphate galactose. Enzymes were also known which could oxidize the glucose and galactose moieties to uridine diphosphate glucuronic and galacturonic acids. The glucuronic but not, so far, the galacturonic nucleotide could be decarboxylated to yield uridine diphosphate xylose, and this substance could undergo epimerization to form uridine diphosphate arabinose. Such reactions could account for the production of most of the sugar units required for polysaccharide synthesis, and synthesis of a number of saccharides had indeed been achieved. One of the first was that of sucrose by the transfer of glucose from uridine diphosphate glucose to fructose-6-phosphate using a wheat-germ enzyme. More recently a preparation from liver had been shown to catalyse transfer to glycogen of D-glycosyl groups, which were joined by α1,4 links. A similar type of reaction had also been demonstrated with starch by preparations from potatoes and beans. Hassid and his colleagues in an attempt to synthesize cellulose obtained a glucose polymer in which the units were joined through the β1–3 positions and which was analogous to the laminarin of seaweeds. Constituent units of mucopolysaccharides also formed sugar nucleotides, and with a preparation from a streptococcus the incorporation of tritiated sugars into hyaluronic acid had been achieved, from tritiated uridine diphosphate glucuronic acid and uridine-diphosphate N-acetyl D-glucosamine, with a net increase in hyaluronic acid. This work on sugar nucleotides and their reactions had made it possible to predict new routes of synthesis for polysaccharides, particularly the formation of the "backbone" chains. There remained, as problems for to-morrow, the realization of such syntheses, and the understanding of how the detailed arrangement and selection of the numerous possible monomers were regulated by the enzymes associated with nucleotides and the many other enzymes involved in a total synthesis.

FOETAL ABNORMALITY

CONFERENCE AT R.C.O.G.

A scientific meeting on the recognition and treatment of foetal abnormality, convened by Mr. A. J. WRIGLEY, was held at the Royal College of Obstetricians and Gynaecologists on March 24. The meeting was opened by the president of the College, Mr. ARTHUR BELL.

The chairman of the morning session, Dr. AGNES MACGREGOR, said she thought the choice of subject specially appropriate. Up to 1950 perinatal mortality had fallen rapidly, but over the past decade this downward trend had checked and in some years perinatal mortality had even risen. We could not accept that this was because an irreducible figure had been reached, for other countries had lower figures. The subject of congenital malformation had become progressively more important because foetal mortality and morbidity from other causes had decreased. There was now a much more hopeful outlook for the victims of malformations.

Increasing Frequency

Professor T. MCKEOWN (Birmingham) reviewed the changes in the distribution of mortality according to age. Now individuals tended to die either pre-natally or in the post-reproductive period. Furthermore, the causes of death after the reproductive age were not due to selection. The frequency of congenital malformations in Scotland had doubled over the past decade and there were marked regional and national differences. It was important to follow all children to the age of 5 years, when the number of abnormalities diagnosed became more frequent. About one in five of all children with congenital malformations died at birth and half were alive at 5 years, though obviously the mortality varied with the type of malformation. The mortality with even minor malformations (e.g., talipes and cleft palate) was distinctly higher than in normal infants. Discussing environmental influences in relationship to anencephaly, Professor McKeown said there appeared to be independent associations with the age of the mother and with the birth order of the child. The incidence of anencephaly was also 50% higher in December and January than in midsummer, and this was independent of birth order or social class. There seemed no association between the seasonal variation and the incidence of poliomyelitis and influenza.

Fatal Defects

Dr. A. E. CLAIREAUX (London) discussed perinatal mortality in the light of the current perinatal survey. The most common fatal defects seen were those of the central nervous system, anencephalics forming the majority. Alimentary defects ranked second, followed by abnormalities of the cardiovascular system, but about one-third of all fatal cases were found to have abnormalities involving more than one system.

Dr. A. C. STEVENSON (Oxford) described some of the genetic facets. Gross abnormalities were not simply due to inheritance; environmental influences on the developing embryo were probably stronger, though this did not mean that genetic factors, which accounted for about 10% of abnormalities, could be ignored. We were still extremely ignorant about the resting phase of the human oöcyte at the stage when it was most vulnerable to damage and abnormal genetic division. He entered a plea for the large-scale collection of data about offspring of consanguineous marriages.

Significance of Hydramnios

A series of 153 infants born at Queen Charlotte's Hospital and dying from malformations of the central nervous system was reviewed by Professor J. H. M. PINKERTON (London). This series comprised 60% of all the fatal malformations, and one or more abnormalities in another

system were present in almost half the cases. In general the antenatal diagnosis was not satisfactory, only half the cases being detected prior to delivery. The significance of hydramnios and its association with pulmonary hypoplasia was mentioned.

Mr. J. S. SCOTT (Liverpool) commented upon the association of hydramnios with atresia of the upper alimentary tract, the hydramnios usually being diagnosed by the obstetrician. In Liverpool the incidence of hydramnios was about 7 per 1,000. From 318 cases of hydramnios there had been 131 monsters and 187 apparently normal children. Hydramnios appeared to be associated with obstruction of the upper alimentary canal, and it was now routine to pass an oesophageal tube on all such neonates. In the discussion which followed Dr. H. G. KOHLER (Birmingham) reiterated that all babies born in association with hydramnios should have an oesophageal catheter passed at birth.

Dr. VICTORIA COFFEY (Dublin) had found that the incidence of anencephaly in Dublin was much higher than in most other centres. There appeared to be a predominance of blood Group O in these cases. No history of consanguinity had been obtained in any of the parents. Mr. W. G. MILLS (Birmingham) divided anencephalics into those which produced gross hydramnios and were born before term, and those which showed no hydramnios and continued to grow, even causing dystocia from their large shoulders. Many other contributions were made to the discussion and the speakers replied to points raised.

Early Diagnosis

In the afternoon the chair was taken by Mr. G. F. GIBBERD (London) and the first speaker, Dr. J. P. M. TIZARD (London), discussed the early diagnosis of the group of congenital defects in which the abnormality was not obvious but of serious consequences, and in which some treatment was possible. With future advances in neonatal cardiovascular surgery many more babies would be amenable to treatment, but most of the lesions were highly complicated and called for an accurate medical diagnosis before surgery could be undertaken. He also stressed the importance of early diagnosis in metabolic diseases.

Professor A. W. WILKINSON (London) spoke on the possibilities of modern paediatric surgery. The mortality of operations in this field was still high and surgery was often limited by delay in diagnosis. Routine examination of the neonate and early diagnosis of congenital defects were therefore most important. The neonate stood surgery extremely well and these patients should be transferred early to units where there were surgeons, anaesthetists, and, above all, highly trained nurses skilled in the management of this type of case. Dr. R. G. CROSS (Dublin) read a short paper on the management of patients who had previously borne anencephalic babies.

Spina Bifida

The neurosurgical approach to deformities of the central nervous system was described by Mr. D. M. FORREST (London). In gross forms of spina bifida we were bound to do as much as possible to ease the burden for the child and its parents. Survival must be anticipated in all but the grossest abnormalities. Where the cord was exposed or there was a thin membranous sac covering the cord, surgery was urgent before infection supervened. If a tough skin covered the defect, emergency surgery was not indicated but early investigation of the neurological damage was an advantage. The long-term results of early surgery depended upon the severity of the original lesion, and in those where the residual paralysis was slight and hydrocephalus did not develop the prognosis was good. In the most severe cases —the minority of those seen—the child would never be able to stand and some died of uraemia, but the best chance of giving these children a reasonable life, and helping their parents, was to institute early treatment. Sir ANDREW CLAYE then commented briefly on the difficult ethical problems presented by these children.

The meeting was closed by Mr. BELL with a vote of thanks to all the speakers.

STATEMENT BY ALCOHOL AND ROAD ACCIDENTS COMMITTEE

The Association's Committee on Alcohol and Road Accidents[1] *met on April 6, under the chairmanship of Dr. R. D. Summers, to discuss the Road Traffic Bill.*[2] *Afterwards the following statement was issued to the press.*

"The Alcohol and Road Accidents Committee of the B.M.A. held a special meeting to-day to discuss those parts of the new Road Traffic Bill concerned with the drinking driver. If this Bill is accepted in its present form and the Courts have to decide whether a person's ability to drive properly 'is for the time being impaired,' the Committee hopes that attention will be paid to conclusion No. 9 of its Report published in January, 1960,[3] concerning the highest concentrations of alcohol in the blood of a driver which can be accepted as entirely consistent with the safety of other road-users.

"Whatever chemical tests become part of routine procedure in deciding the degree of drunkenness, clinical examination by a doctor must remain an essential part of the investigation. The Bill says that blood tests may be taken as part of the investigation. But the Committee feels this is generally unnecessary, because urine tests serve equally well.

"The Committee believes that methods of analysing samples of blood, urine, or breath should be standardized, and that evidence should be given only by analysts sufficiently experienced in those methods.

"It should be for the doctor to decide whether a suspect's condition in the police station for any reason is such that his consent can be properly given to a sample being taken."

[1] Chairman: Professor E. J. Wayne.
[2] See *Brit. med. J.*, 1961, **1**, 973.
[3] See *Brit. med. J.*, 1960, **1**, 269. Conclusion No. 9 reads: "The Committee considers that a concentration of 50 mg. of alcohol in 100 ml. of blood while driving a motor vehicle is the highest that can be accepted as entirely consistent with the safety of other road users. While there may be circumstances in which individual driving ability will not depreciate significantly by the time this level is reached, the Committee is impressed with the rapidity with which deterioration occurs at blood levels in excess of 100 mg./100 ml. This is true even in the case of hardened drinkers and experienced drivers. The Committee cannot conceive of any circumstances in which it could be considered safe for a person to drive a motor vehicle on the public roads with an amount of alcohol in the blood greater than 150 mg./100 ml."

Nova et Vetera

LAENNEC AND HIS TIMES

"Surely if Laennec could hear sounds in a chest with no more assistance than a roll of paper you can do better with that new-fangled binaural of yours." Thus spoke my chief on his ward rounds, waving his own beloved wooden stethoscope. In those days, to most of us, Laennec meant little more than the discoverer of the stethoscope.

Dr. Kervran has given us a beautifully written and factual biography* of this outstanding son of Brittany, which brings into proper perspective his remarkable genius and gives him just credit for so much more than being the mere inventor of a useful adjunct to his already remarkable professional skill. That Laennec was a genius there is no doubt; his versatility, his

**Laennec. His Life and Times.* By Roger Kervran, M.D. Translated from the French by D. C. Abrams-Curiel. (Pp. 213+x. 21s.) Oxford, London, New York, Paris: Pergamon Press. 1960.

capacity for skills outside pure medicine, are well related in this book. Living, as he did, for 45 years through the French Revolution, the Vendée wars, and the Restoration Laennec had much to contend with apart from his ambition to rise to eminence in his chosen profession.

If the tuberculous type exists, it seems inevitable that Laennec himself should be a sufferer from the White Plague. His whole attitude to life, his amazing spirit, which maintained and sustained a weakly body, was typical of the consumptive. Perhaps it was this very fact which provided him with the incentive to study phthisis.

Dr. Kervran has very rightly chosen to be free in his translations of the original documents, but he has contrived a descriptive level which leaves no doubt of the character of the man he writes about. Indeed, without himself possessing a very keen knowledge of Brittany and the Breton tongue he could not have produced such a pluri-pharmacopoeial mixture of so many ingredients and so few incompatibles. There is no nasty deposit in this medicine, the inscription might well be: The mixture to be taken as often as possible. The main characters stand out in perfect profile, the aspirations, disappointments, and successes of the principal figure are beautifully drawn. Perhaps a little map of Brittany would have added interest to the text. Dr. Kervran is to be congratulated on having given us such a readable book which is not only a life of Laennec but an excellent account of the troubled times in which he lived and worked. J. C. A. DOWSE.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Phenylpyrrolidinopentane

"Villescon" (Boehringer).

Chemistry.—Villescon contains 1-phenyl-2-pyrrolidinopentane hydrochloride. This substance may be regarded as having been formed by opening the isoquinoline ring of the papaverine molecule and replacing one of the two aryl radicles by an aliphatic chain containing five carbon atoms. In addition, vitamin-B complex and vitamin C are included.

Pharmacology.—There is some pharmacological evidence that in the experimental animal appetite, respiration, blood-pressure, and cerebral functions are stimulated. It is thought that some of these effects are produced by stimulation of the diencephalon, as there seems to be an antagonism to reserpine-induced sedation. Massive doses in dogs produce organized convulsive movements, which suggest in addition an action on the cerebral cortex. It is claimed, as the result of subsequent clinical investigations—most of which depended entirely on the subjective sensations of groups of patients—that the stimulant effects produced by very large doses in animals are reproduced by small doses in the human subject.

Therapy.—The manufacturers recommend the preparation as a general tonic in convalescence, in various states associated with exhaustion, and as a stimulant in the management of old people. The dose is 1 to 2 tablets first thing in the morning and in the early afternoon. Each tablet contains 10 mg. of the active substance.

Side-effects.—In therapeutic doses no undesirable side-effects have been noted apart from a tendency to sleeplessness in a minority of patients. Villescon is contraindicated in cases of thyrotoxicosis.

N.H.S. Basic Price.—100 tabs., 30s. 2½d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Prognosis in Schizophrenia

SIR,—Whilst I congratulate my old friend and colleague, Dr. Alan Norton, on his most valuable paper, "Mental Hospital Ins and Outs" (February 25, p. 528), he will, I know, forgive me if I venture some criticism of, and a few reflections on, his findings.

My major disquiet relates to the data on which Dr. Norton strikes a more optimistic note on the prognosis in schizophrenia. His optimism, so far as I can determine, rests on twin piers: the improved response to modern methods of treatment, and the increased discharge rate from, or conversely the shorter stay in, hospital. The two are, of course, largely interdependent. Little or no mention is made by Dr. Norton of the natural history of the disease as a factor in prognosis. Schizophrenia is characterized by recurrent remissions and relapses which, needless to say, can occur without any specific treatment. Each relapse wounds the total personality more deeply so that subsequent remissions are less and less complete. At some arbitrary point along the road it is justifiable to term the case "chronic," or "long-term," to use a current euphemism. It is my impression that the effect of modern methods is to precipitate a remission earlier than might otherwise have been expected. But what they seemingly do not do is to prevent relapses. How else can one explain the alarming number of relapses, represented by readmissions, which must include a proportion of the sort of case whose response to treatment would have been classified as "very good." So the patients come back, are further treated with perhaps less satisfactory results, and go again. How often this cycle can be repeated depends on individual cases, but it can be frighteningly frequent. In effect, the "open-door" policy of yesterday has been transmuted into the "revolving-door" policy of to-day. This new policy may or may not be desirable, but it cannot fairly be used as a measure of prognosis. A disease is no less chronic because its manifestations can and do continue outside as well as inside hospital.

The discharge rate as an index of recovery, or even improvement, in mental illness bristles with fallacies. One of the ironies of the enormous and most welcome increase in voluntary (now informal) admission to mental hospitals in recent years is that patients, particularly schizophrenics, elect to leave hospital before they are well enough to do so. Not only may the patients be no better on leaving: they may in fact be worse. Their self-discharge may be an expression of the loss of insight into their illness which prompted them to seek medical help in the first instance; or it may be an act of impulsiveness such as is seen so often in schizophrenics. Furthermore, the discharge rate may be determined by the policy of an individual hospital. Paradoxically enough, a hospital which concerns itself with ensuring work and accommodation for its patients prior to discharge—and this is often difficult and time-consuming—may have a lower discharge rate than one which is less exacting in these respects.

Another major flaw, as I see it, in Dr. Norton's argument is in his failure to follow-up his discharged cases. The only reference I can find to their fate after leaving hospital is in

a somewhat nebulous statement—that is, "At least she is now at home and often at work for the greater part of the time." No idea is given of how many are at home, or how long they have stayed there, or how many are at work. Although ideally home is where the schizophrenic should be, all homes are not ideal. Schizophrenics tend to have strange, if not frankly psychotic, parents or relatives, and their influence may be actually detrimental to the welfare of the patients rather than the reverse. As a corollary of this, if one accepts, as I do wholeheartedly, and indeed as Dr. Norton does by implication, that what he calls "the changed atmosphere of the hospital" has subscribed to the patients' improvement then surely it may militate against their well-being if they are robbed of the props which the hospital affords, unless adequate substitutes at home or in the community are forthcoming.

And what of these schizophrenics who have no homes or no community to support them? In London in particular, with vast, shifting, multi-racial, multi-coloured, and multi-lingual masses, it is by no means uncommon for discharged patients to belong nowhere and so be thrust back on their own resources, which, by virtue of their psychosis, are slender indeed. The problem of this rootless variety of chronic schizophrenic, and, indeed, of others belonging to poorly integrated social groups, cannot be solved by sweeping it out of the mental hospitals under the social mat. Unless and until the community makes adequate provision for the ex-hospital chronic schizophrenics in their midst—and there is no apparent hurry to do so in spite of the recommendations of the Mental Health Act, 1959—they will continue to erupt in a variety of ways. Some undoubtedly will find their way back to hospital—some, less fortunate perhaps, will swell the ranks of the unemployed and unemployable. Others will join the army of vagrants and elbow each other off the park benches, or lengthen the queues outside the doss-houses. Others still will embarrass the courts and prisons where their crimes, usually petty and purposeless, unless interpreted as a plea for care and protection, have landed them.

To illustrate this last point I might add that since the beginning of this year I have been called in by prison medical officers under the terms of the new Act and arranged admission to hospital for no less than 17 male prisoners. All of them are seriously disturbed chronic schizophrenics who have been discharged from mental hospitals, sometimes only a matter of a few days before being apprehended by the police. What the total number of such prisoners is in the country as a whole I have no idea, but it must be very substantial.

Unfortunately, the decision as to whether Dr. Norton's prognostic optimism in schizophrenia, or my scepticism, is justified is of more than academic importance. On the assumption that he is correct in his views, Dr. Norton predicts that the population of mental hospitals will fall by 30% in the next 20 years. Now that the Minister of Health has expressly sentenced the present mental hospitals to destruction, such predictions coming from someone with the prestige which Dr. Norton rightly enjoys might accelerate carrying out the sentence. I only hope that the building of other smaller institutions under whatever guise or name they function, but catering, I suspect, for roughly the same number of mental patients as at present, will precede the onslaught of the bulldozers.—I am, etc.,

Horton Hospital,
Epsom, Surrey.

HENRY R. ROLLIN.

Management of Abortion

SIR,—The abortion unit at Walton has long been the envy of those of us who must nurse our cases in clean gynaecological wards, and Mr. Wilfred S. E. Perera's excellent description (March 11, p. 705) serves also to increase our admiration of its work. Mr. Perera is good enough to compare his cases with my own numerically similar series,[1] and I am happy to see the improvement which can be achieved by the unitary method of treatment. There are, however, a few points on which I would like to comment.

As a convert to the "interventionist" school, I am constantly impressed with the finding of chorionic tissue in cases described as complete. Is there a case for the French system of curettage for all abortions except threatened? Mr. Perera also talks about "a pint or two of blood" for anaemic patients. Surely the single-pint method should be abolished. If a woman needs blood she requires a minimum of two pints (1.1 litres), and, if this is unobtainable, dextran is still a useful stop-gap. I am sorry to see Mr. Perera discarding this preparation because of Scott's adverse experience.[2] Interestingly enough, dextran was first used for this very purpose in my old unit at Dulwich Hospital, and it proved a life-saving measure.

I am also sorry to see the perpetuation of the use of Hega's bougies for the operation of dilatation and curettage. I had hoped that this inefficient, dangerous, and brutal weapon had been universally replaced by the modern graduated instrument. In the hands of even experienced surgeons it can be grossly traumatic, and the junior staff who usually carry out these operations should be protected against it.

The flushing curette should be condemned out of hand, but the actual curette of the apparatus used dry is excellent for the evacuation of retained products—I suspect more efficient than Mr. Perera's. *Every* case should be curetted after the preliminary removal of the large fragments—it is astonishing how often quite large pieces are recovered in this way. Sharp curettage is quite safe when an oxytocic is used, though I prefer direct intrauterine "pitocin" (oxytocin) injection since this method was first shown me by V. B. Green-Armytage several years ago.

These are small points of criticism of an otherwise excellent paper. The point of real importance is the urgency of the whole problem. The abortion case is universally regarded as "dirty," to be admitted reluctantly. Most teaching hospitals, indeed, refuse them absolutely, so that students rarely see this most frequent complication of pregnancy. But we are not moralists, and have no right to give anything but the most prompt service to these often seriously ill women. The solution lies in the institution as soon as possible of abortion units of the Walton type. We have the example, and the cost is negligible in comparison with the improvement in the ultimate results.—I am, etc.,

London W.1. ALBERT DAVIS.

REFERENCES
[1] Davis, A., *Brit. med. J.*, 1950, **2**, 123.
[2] Scott, J. S., ibid., 1955, **2**, 290.

Phenylketonuria

SIR,—The publication of three most interesting articles on phenylketonuria (March 18) prompts me to put on record the results obtained in the treatment of this condition in Liverpool, where we have been

fortunate to make the diagnosis in three children under the age of 6 weeks.

Eleven cases of phenylketonuria have come under my care for treatment. In five the diagnosis was made too late for any benefit to accrue, and treatment has been stopped. One boy, treated from the age of 11 months, has shown marked behavioural improvement. Though his I.Q. has not risen above 50, treatment seems well worth while, and he may eventually be suitable for training in an occupation centre. A girl accepted for treatment at the age of 3 has also shown considerable improvement in her general behaviour, becoming quieter, easier to manage, and during the past 12 months her vocabulary has increased; the benefits, however, are not striking. Another girl started treatment at the age of 11 months, at which time she was obviously retarded; now, after 14 months of treatment, during which time her serum phenylalanine has remained consistently below 3.5 mg. per 100 ml., she is accepted by most people as being a normal child; her I.Q. is approximately 80.

The three cases in whom very early treatment was possible deserve reporting in more detail.

Anthony was under observation from birth because one of his two brothers was known to be a phenylketonuric idiot. He was born in April, 1957. At the age of 3 weeks his urine first gave a positive ferric chloride test. A sample of blood obtained about this time was kindly analysed by Dr. L. I. Woolf, who reported it to be diagnostic of phenylketonuria. Treatment was started on the 27th day of life, and has been maintained ever since. Serum phenylalanine estimations have been performed in Alder Hey Hospital since November, 1957, and regular estimations every four to eight weeks have shown that Anthony's blood level has almost invariably been below 3 mg. per 100 ml. He is accepted by his family and neighbours as a normal child. His development quotient is estimated to be 80. If his present progress is maintained he should be able to satisfy the educational standards of a normal school. At the age of 3½ his weight was 34 lb. (15.4 kg.).

Brenda was born in July, 1958, and was under observation from birth because phenylketonuria had previously been diagnosed in one of her two sisters. Her serum phenylalanine on the ninth day of life was 13 mg. per 100 ml. Treatment was started when she was 11 days old, and has been maintained ever since. Apart from one lapse in the administration of the diet due to difficulties at home, her serum phenylalanine has remained within normal limits. Her I.Q. at the age of 2 was 80 and she is continuing to do well. Her progress in the first year of life was interrupted by severe gastroenteritis followed by megaloblastic anaemia, when some vitamins were inadvertently omitted. Her weight at 12 months was consequently only 15¼ lb. (7.9 kg.). At 2 years and 4 months she weighed 26 lb. (11.8 kg.).

Brendan, when visiting a child welfare clinic in the City of Liverpool at the age of 24 days, passed urine into the pan of the weighing-scale. A "phenistix" test was performed and found to be positive. His serum phenylalanine was 27 mg. per 100 ml., and he started treatment on the 25th day of life. Seven days later the serum phenylalanine level was 11 mg. per 100 ml., and on the 15th day after starting treatment it was 3.2 mg. per 100 ml. Since then monthly estimations have always given a result below 3.5 mg. per 100 ml. He has not been given formal psychological testing, but all his attainments as judged by a paediatrician are within normal limits. He is now 11 months old and weighs about 24 lb. (10 kg.).

The usual line of treatment has been adopted for all patients comprising mainly "cymogran," wheat starch, butter or margarine, fruit, and vegetables, with regulated quantities of milk and potato to provide the necessary phenylalanine. All the babies accepted the diet without difficulty, not having had time to develop taste prejudices. Anthony, now at the age of 3½, regards cymogran as a normal and proper article of his diet. A phenylalanine low amino-acid mixture prepared from bovine serum (Scientific Hospital Supplies Ltd., Liverpool) is at present under investigation; it has been accepted well by several patients, and may prove useful in the long-term treatment.

I cannot provide graphs showing the change in I.Q. in my patients. Regular psychometric testing is of course of great interest, but, as Mr. Stephen Coates (March 18, p. 767) says, not of great predictive value. The true assessment of the value of treatment will come when the patients face the problems of school.

One other patient deserves special mention. Karen, at the age of 3 years, had an I.Q. of about 50. Her urine contained all the substances associated with typical phenylketonuria, but her serum phenylalanine was only 2.5 mg. per 100 ml. It rose to a maximum of 7.2 mg. per 100 ml. after she took 2.8 g. phenylalanine by mouth. A second phenylalanine tolerance showed a similar rise, and curiously her serum tyrosine also rose from 0.5 to 1.55 mg. per 100 ml. She evidently retains some power to convert phenylalanine to tyrosine, and may even be a heterozygote. Investigations on this child and her parents are still in progress. I have not found a similar case in the literature, and will be interested to know whether one exists.

Unfortunately, Mr. Coates has followed the lead given by Knox,[1] and groups together all cases in whom treatment was started under the age of 14 months. I think that this is unfortunate, because many phenylketonurics are severely retarded by the age of 12 months and little improvement can then be expected. In my opinion, the time has now come to collect information on all cases in whom treatment was started under the age of 6 months. The total number of cases is not large—Knox only finding 11 in the published literature up to 1959—so it is desirable that anyone who has treated even one case from an early age should report it with full details without waiting for sufficient material to make a full-length article. It might be useful to establish in this country a central registry where information on these patients could be collated. The excellent work reported by Dr. Mary M. M. Boyd (March 18, p. 771) from Birmingham deserves notice, and shows that in the future many more cases should be detected and treated at an early age. All praise to the Birmingham health visitors and to those who stimulated and maintained their enthusiasm.—I am, etc.,

F. P. HUDSON.

Alder Hey Children's Hospital,
Liverpool 12.

REFERENCE

[1] Knox, W. E., *Pediatrics*, 1960, **26**, 1.

Routine Lumbar Radiography

SIR,—A routine *x*-ray of the lumbar spine has been taken in all cases of acute low lumbar backache seen in the sorting-room at St. Thomas's Hospital in the past, and this has been general practice in many centres. On looking into the value of these *x*-rays I now believe that routine *x*-rays should be abandoned.

Among any large series of cases of low backache there will be undoubtedly the odd case of malignant disease or inflammation of a vertebra, but I believe that these cases can be suspected clinically, as they do not present as classical cases of acute prolapsed intervertebral disk. The examination and history must be

complete and an examination of the breasts in the female and a rectal examination must always be included. If it is possible to abandon routine *x*-rays of the lumbar spine, and I believe it is, then a great deal of money can be saved and many patients can be spared unnecessary irradiation.

Cases of sudden onset of acute lumbar backache of recent origin with typical distribution of sciatic pain, in an otherwise fit patient, can be treated initially by manipulation if there are no signs of nerve-root palsy, or by traction if there are abnormal neurological signs. I believe that an E.S.R., which costs much less than an *x*-ray, will often be helpful if there is any doubt that a more serious lesion than acute prolapsed intervertebral disk exists. The test is normal in disk lesions, but is significantly raised in active tuberculosis or malignant disease. If malignant disease is present, it is most unusual for the case to present as a classical disk lesion. There is usually evidence of the primary lesion in the breast, bronchus, kidney, or prostate. Even if there are no signs in these regions the history is suggestive of disease in one of these systems.

Reports of *x*-rays which comment on spina bifida occulta, sacralization of L.5, osteophytosis, slight diminution of the disk space, etc., do not influence the course of treatment initially. The vast majority of cases of acute lumbar backache which are seen in the sorting-room recover within three weeks and are never seen again. These patients do not require *x*-ray. If treatment fails or there is anything suspicious in the signs or history of the case, then an E.S.R., followed if necessary by an *x*-ray, is indicated.—I am, etc.,

St. Thomas's Hospital, London S.E.1. D. J. REID.

Personality and Lung Cancer

SIR,—In a previous paper[1] it was concluded that, as compared with non-smokers, cigarette-smokers were (1) more extraverted, (2) slightly less rigid, and (3) slightly more subject to neuroticism but not significantly so. If lung-cancer patients are a random selection of cigarette-smokers with equal probability of selection per cigarette smoked, then their characteristics as regards extraversion, rigidity, and neuroticism respectively ought not to differ significantly from those of cigarette-smokers generally, for these characteristics had a gradient related to the amount smoked.

Using the short form of the Maudsley Personality Inventory, an analysis of 116 lung-cancer patients and 123 control patients seen in hospital has revealed the following:

(*a*) In regard to extraversion there is, over all patients, no significant difference between the lung-cancer patients and controls. Further, if both groups are divided according to whether they had or had not a past history of psychosomatic disorders, there is still no significant difference between lung-cancer and control patients *without* past history of psychosomatic disorder, but in patients *with* a past history of psychosomatic disorder lung-cancer patients tended to be more extraverted than control patients.

(*b*) When we turn to neuroticism, however, the picture is contrary to expectation, as the lung-cancer patients have *much less* neuroticism than the control patients. Moreover, if both groups are again divided according to whether they had or had not a past history of psychosomatic disorder, it is found that in those without a past history of psychosomatic disorder lung-cancer patients had *less* neuroticism than the controls, and similarly among those with a past history of psychosomatic disorder.

The actual scores were as follows:

	Lung-cancer Patients		Controls	
	Without Past History of Psychosomatic Disorder	With Past History of Psychosomatic Disorder	Without Past History of Psychosomatic Disorder	With Past History of Psychosomatic Disorder
	Mean SD	Mean SD	Mean SD	Mean SD
Extraversion	7·41±2·71	7·77±2·61	7·48±2·91	6·59±3·05
Neuroticism	3·00±3·39	3·74±3·50	4·86±3·89	5·31±4·12
No. of patients	59	57	69	54

This evidence, therefore, suggests that in fact lung-cancer patients are *not* a random sample of smokers. Moreover, the lung-cancer patients with a past history of psychosomatic disorders are not a random sample of people with common psychosomatic disorders, since, as compared with Sainsbury's figures[2] for such people, lung-cancer patients were less neurotic and more extravert.—We are, etc.,

DAVID M. KISSEN.
University Department of Psychological Medicine, Southern General Hospital, Glasgow.
The Maudsley Hospital, Denmark Hill, London S.E.5. H. J. EYSENCK.

REFERENCES
[1] Eysenck, H. J., Tarrant, M., Woolf, M., and England, L., *Brit. med. J.*, 1960, **1**, 1456.
[2] Sainsbury, P., *J. psychosom. Res.*, 1960, **4**, 261.

Oral "Persantin"

SIR,—Dr. D. C. Deuchar's letter (April 1, p. 967) confirms the results obtained by uncontrolled clinical trial of "persantin" in this practice since it became generally available on February 27. Of five patients with angina pectoris treated with oral doses of 50 mg. t.i.d., none reported any improvement in the number or severity of attacks of pain. In two cases the drug had to be withdrawn after only a few days because of the occurrence of much more frequent attacks of pain at rest, and in one because of constant upper substernal pain, worse on exercise, which started the day after beginning treatment, and disappeared completely by the second day following its cessation. These three cases were greatly improved subsequently by a long-acting preparation of pentaerythritol tetranitrate.

A week ago, the manufacturers' representative called and expressed astonishment when given details of the cases, saying that the drug had been their major selling product in Germany and elsewhere for the past year, and he knew of no adverse reports. Dr. Deuchar's results are equally disturbing in the face of such optimistic advertising, and I should like to reinforce his suggestion that further clinical assessment is necessary before the drug is more widely used.—I am, etc.,

Salcombe, Devon. HAROLD STANLEY.

SIR,—Following upon the letter from Dr. D. C. Deuchar (April 1, p. 967), I feel I should point out that we, too, carried out a double-blind clinical trial of this drug in oral dosage of 25 mg. four times a day at the request of the manufacturers, and also obtained an entirely negative result. This result will be published very shortly in detail in the *Scottish Medical Journal*, but the results have in the meantime been communicated to the manufacturers, who acknowledge them in much the same terms as they employed to Dr. Deuchar. They have, however, marketed the product nevertheless.—I am, etc.,

Royal Victoria Infirmary, Newcastle upon Tyne. H. A. DEWAR.

SIR,—Dr. D. C. Deuchar's letter (April 1, p. 967) draws attention to the well-recognized difficulty of assessment of the effect of drugs used in the treatment of angina pectoris. He refers in his first paragraph to "persantin," which is marketed by my company, as a drug "which it is claimed, largely on the basis of work in experimental animals, to be effective as a coronary vasodilator." This could, I feel, have been more accurately expressed. Persantin *is* effective as a coronary vasodilator. Studies in the animal and in the human subject with healthy coronary trees have demonstrated this without doubt.[1–5] The question at issue is whether persantin is equally effective in the diseased coronary tree.

Dr. Deuchar's own series is, as he admits, small, involving only six patients, and the maximum length of time during which any patient was treated with persantin was a little over six weeks (52 days). The symptom used for assessment was the incidence of attacks of angina—a criterion which has been shown in the case of many other accepted coronary vasodilators to give misleading results. I would refer to the work of Cole *et al.*,[9] in which the effects of triethanolamine trinitrate, calcium theophyllinate, pentaerythritol tetranitrate, and chlorpromazine were assessed in the treatment of angina pectoris, and compared with placebos, on a series of patients over a period of two years. At the end of this time the authors reported, "None of the drugs could consistently be distinguished from its placebo by doctors or patients on the basis of its effectiveness in decreasing chest pain." They quote Katz,[10] who says, "Angina pectoris is a variable subjective manifestation with little consistent quantitative relation to the underlying coronary disease, and little correlation with electrocardiographic changes under the stress of exercise . . . Angina pectoris is pain, and in this sense, must be analysed in terms of physiology of sensation, quite apart from factors having to do with coronary flow." The article by Dr. J. R. A. Mitchell (March 18, p. 791) on the lack of correlation between objective and subjective assessments of angina amply confirms this point and serves to illustrate the difficulty of evaluating drugs in this condition. Simply because a controlled trial based on doubtful criteria does not demonstrate an effect we would be unwise to condemn a treatment out of hand.

When objective criteria, such as the normalization of electrocardiographic changes in myocardial ischaemia, are employed, we may expect more objective results. Using such criteria, many authors[3–7] have shown that persantin is effective, and more direct evidence has been adduced by cardiac catheterization studies that intravenous persantin has been able to increase the coronary flow.[2] This last work has been repeated and confirmed in the United Kingdom,[8] and a publication reporting these results is expected in the near future. The same author[8] has shown that intravenous persantin has modified the cardiographic pattern and even abolished ischaemic changes in cases of coronary artery disease.

Persantin has been used by cardiologists and general physicians in countries all over the world for the past two years, and few drugs have been so extensively investigated. Are we to assume that these clinicians have continued to use the drug in the face of manifest inactivity? Reports on the effectiveness of persantin have been published by such centres as the University of Marburg, Tübingen, Cologne, and Milan, many of them referring to series of up to 200 patients treated for as long as two years. Can the cardiologists at these centres all be deluded about the actions of persantin?

I fully realize and appreciate the preference of British clinicians for published evidence emanating from investigators of their own country. Nevertheless, Sir, we cannot consistently decry the work of our colleagues abroad. Forty-six publications have appeared to date on the subject of persantin, and more than 40 of these have clearly demonstrated its effectiveness. Positive results achieved in this country are at present awaiting publication. One of them[8] shows that increases in coronary blood flow of up to 36% are produced by intravenous persantin, as demonstrated by cardiac catheter studies, and improvement in abnormal E.C.G.'s in myocardial ischaemia has already been referred to. It is evidence such as this which has led my company to market persantin, and this decision, and the doses recommended, are the result of long deliberation and assessment of this evidence.—I am, etc.,

Sandwich, Kent. F. J. A. BATEMAN,
Director of Medical Services,
Boehringer Ingelheim Division, Pfizer Ltd.

REFERENCES

1. Kadatz, R., *Arzneimittel-Forsch.*, 1959, **9**, 39.
2. Knipping, H. W., Bolt, W., and Mikulicz, F., ibid., 1960, **10**, 364.
3. St. Grief, *Wien. med. Wschr.*, 1960, **110**, 463.
4. Bambor, H. J., *Med. Klin.*, 1960, **55**, 1155.
5. Pabst, H. W., ibid., 1959, **54**, 257.
6. de Castro, B., and Parchi, C., *G. Clin. med.*, 1960, **41**.
7. Fischer, E. K., and Fiegel, C., *Dtsch. med. J.*, 1959, **10**, 484.
8. Peel, A. A. F., personal communication.
9. Cole, S. L., Kaye, H., and Griffith, G. C., *Circulation*, 1957, **15**, 405.
10. Katz, L. N., *Amer. Heart J.*, 1935, **10**, 322.

Acute Diabetic Abdomen

SIR,—Within the last few months I have seen several cases of what are best described as the "acute diabetic abdomen." These cases have all been seen in surgical wards and present with vomiting and upper abdominal pain, and simulate one of the acute abdominal surgical emergencies. I do not think either surgeons or general practitioners are fully aware that this condition exists, and the object of this letter is that it may be drawn to their attention through the medium of your columns. It is, of course, a condition of diabetic pre-coma with ketosis and requires the most urgent medical treatment, as for diabetic coma, as all those physicians who deal with diabetics are well aware. Admission to surgical wards almost invariably results in delay in this treatment being instituted, and this could prove to have the most dire consequences for the patient. Fortunately, this has not occurred in any of the cases that I have recently seen, but it has meant treatment being delayed.

Unfortunately, medical students do not seem to be taught its existence, and therefore any failure to recognize it by those who are not constantly treating diabetics is very understandable. As I have already said, a desire to make it more widely known is what has prompted me to write this letter.—I am, etc.,

Diabetic Clinic,
Royal Gwent Hospital,
Newport, Mon. P. EDWARD DIPPLE.

Hypoglycaemic Coma from Chlorpropamide

SIR,—When a diabetic is put on insulin or one of the oral hypoglycaemic agents he is usually warned about the signs of overdosage and the circumstances in which it is likely to arise. The following case illustrates the need to give these warnings when the drugs are used for conditions other than diabetes.

The patient, a boy aged 18, was admitted to hospital on January 7. He had been having anti-tuberculous treatment at home for six months. A chronic cough had been more marked for the previous two weeks, and three days before admission he had complained of a "cold," with sweating, nasal discharge, and general malaise. He was put to bed and given broad-spectrum antibiotics by his doctor. For several months he had been complaining of headaches.

On the day before admission he had seemed rather better and was told that he could get up the next day. On the day of admission the patient's mother had found him unconscious in bed with the light on, suggesting that he may have been unconscious since the previous night. His doctor thought that this might be a case of tuberculous meningitis and the patient was admitted to the fever unit. No history was obtained from the parents of any drugs having been taken other than P.A.S. and isoniazid.

On Examination. — Deeply unconscious; stertorous breathing; responding only to painful stimuli. Acne vulgaris of the face and back. Not sweating. Slightly clammy. Temperature normal. *C.V.S.* — B.P. 104/70. Pulse 60 per min. Occasional ventricular extrasystoles. Heart sounds normal. *R.S.*—Percussion note resonant. Breath sounds normal. *Abdomen.*—N.A.D. *C.N.S.*—Pupils equal, responded briskly to light. Eyes moving from side to side. Fundi: disk margins clear, no evidence of papilloedema or haemorrhages. Reflexes: equal both sides, very brisk; both plantar reflexes extensor. There was some voluntary movement in all limbs on painful stimuli. Marked spasticity of all limbs. No neck stiffness.

Re-examination of the C.N.S. later showed no response to painful stimuli; pupils equal, reacting to light; conjugate deviation to the left. Increased muscular tone on left side. Reflexes now brisker on the left than the right, both plantars extensor. Breathing laboured. Some slight sweating. Lumbar puncture was performed and gin-clear fluid under normal pressure with free rise and fall was obtained. Laboratory report on C.S.F.: protein—15 mg./100 ml.; globulin—no excess; sugar—45 mg./100 ml.; no cells seen.

In view of the negative findings in the C.S.F. and the absence of papilloedema, the basic cause of the coma was thought not to lie in the C.N.S. The blood sugar was reported as 57 mg./100 ml. In view of this the patient was given 20 ml. 50% dextrose and immediately recovered consciousness. He denied having taken anything unusual in the way of drugs, and it was thought possible that he might either have some form of adrenal crisis or an insulin-secreting tumour of the pancreas. However, his doctor rang up to furnish further details of treatment and reported that the patient had been attending a skin clinic for treatment of his acne, and that for the past two months he had been taking chlorpropamide 250 mg. b.d. For a few days preceding the attack of unconsciousness he had not been eating so much as usual and had taken his last tablet late in the evening, several hours after his last meal.

On further observation in hospital he remained perfectly well. It was thought that the cause of the coma was an overdose of chlorpropamide.—I am, etc.,

St. Nicholas Hospital,
London S.E.18.

K. TRICK.

Functional Efficiency of Circle of Willis

SIR,—Dr. C. J. Dickinson (March 25, p. 858) suggests that, in considering reconstructive surgery for atheroma of carotid and vertebral vessels, the state of all our four arteries should be borne in mind. Few would disagree with this general conclusion. However, it is important to analyse the method and results which led Dr. Dickinson to this conclusion, since this article is one of a series based on the same perfusion method in cadavers and the implications of these results might be of considerable importance.

Dickinson and Thomson[1 2] perfused arteries via a length of rubber tube, 8 mm. in diameter and 295 cm. long, through cannulae of six different sizes, with an overall pressure drop of 140 mm. Hg. The authors have used "total flow rate" as the parameter for comparing the arteries, and have made no correction for tubing or cannula resistance. This procedure is valid only if the resistance of the tubing and cannula is either constant or negligible when compared with the resistance of the artery.

It can in fact be calculated from the authors' data that the resistance offered by tubing and cannula averaged about 66% of the resistance of the artery alone, ranging from 7% to 1,250%. The authors made no correction for this factor and give no experimental data to support this omission; nor does it seem justified in view of the magnitude of these variations. The total flow rate, or "fluid-carrying capacity," used by the authors as a parameter for comparing arteries must therefore be suspect and the calculated resistance of the artery alone should be used. A corrective factor therefore needs to be applied to the data on page 858 before conclusions can be drawn from them.

It is possible to make an approximate estimate of the resistance due to the artery alone. If we assume flow to be laminar and not turbulent, a precise calculation would be possible, but it can be shown, for example, that in most of the vertebral arteries turbulence would occur at flow rates in excess of 6 ml./sec.—that is, in the majority of cases. (This figure is based upon an artery diameter of 3 mm. and a viscosity of 1.15 centipoises for 5% ammonia at 15° C.) This turbulence prevents accurate estimate of the resistance of the artery.

An even more serious objection arises in trying to extrapolate these results in cadavers to conditions *in vivo*. Arteries are elastic structures and do not have an absolute resistance to flow, but will produce resistance varying with the degree of stretch applied to the walls—that is, with the internal distension present. The mean internal distension pressure used in the cadavers can be calculated from the mean pressure used throughout the whole circuit (70 mm. Hg.) and the average resistance of the arteries. It was between 40 and 50 mm. Hg. compared with 117 mm. Hg. for the average mean blood-pressure of the same patients before death. The average flow rates used (4.2 litres/min. for all four cerebral vessels) and the distension pressures were thus widely different from conditions obtaining in life. The results of these experiments need some other confirmatory evidence before they can be accepted as being of physiological significance. A direct test of their validity is difficult to obtain, since it is not easy to measure resistance in the carotid and vertebral trunks in living subjects, but an indirect test can be applied.

If the perfusion data on cadavers represent variations in resistance in vertebrals and carotids in life, then, from graphs in Dickinson and Thomson's[1 2] papers, the following should be true.

(*a*) In normal patients there should be a significant pressure gradient along the main carotid and vertebral trunks.

(*b*) In patients with essential hypertension and patients with stroke there should be a proportionately larger pressure gradient between the brachial artery and the circle of Willis.

(*c*) Patients with renal and malignant hypertension should have higher pressure in the circle of Willis than patients with essential hypertension.

Bakay and Sweet,[3] Woodhall *et al.*,[4] and Bloor *et al.*[5] have taken simultaneous pressure measurements by intra-arterial needle in the cervical carotid and the circle of Willis and its branches. Bakay and Sweet[6] have also taken readings from the vertebral artery. The pressures in the circle of Willis were over 90% of the pressures in cervical carotids or vertebral artery, even in hypertensive patients. I have obtained similar results using retinal artery pressure readings as an indirect estimate of pressure in the anterior part of the circle of Willis and comparing these with brachial artery pressure readings in 150 patients. The ratio retinal artery pressure/brachial artery pressure did

not differ significantly among normotensives, patients with stroke, patients with renal or malignant hypertension, and patients with essential hypertension (this work is at present being prepared for publication).

The available evidence therefore provides no support for the belief that the post-mortem data of Dickinson and Thomson have *in-vivo* significance. The low "fluid-carrying capacity" that these authors find in perfusion experiments in cadavers, which Dr. Dickinson calls "stenosis," bears little relationship to carotid or vertebral "stenosis" as clinicians and radiologists use the term, and it is therefore unwise to draw clinical conclusions from these data.—I am, etc.,

ROBERT LOWE.

University College Hospital Medical School, London W.C.1.

REFERENCES

1 Dickinson, C. J., and Thomson, A. D., *Clin. Sci.*, 1960, **19**, 513.
2 —— Ibid., 1961, **20**, 131.
3 Bakay, L., and Sweet, W. H., *Surg. Gynec. Obstet.*, 1952, **95**, 67.
4 Woodhall, B., Odom, G. L., Blood, B. M., and Golden, J., *Ann. Surg.*, 1952, **135**, 911.
5 Bloor, B. M., Odom, G. L., and Woodhall, B., *A.M.A. Arch. Surg.*, 1951, **63**, 821.
6 Bakay, L., and Sweet, W. H., *J. Neurosurg.*, 1953, **10**, 353.

Farmer's Lung Again

SIR,—We have seen with interest your leading article on this disease (March 11, p. 727) and can confirm from our own practices that during the past winter cases have been more prevalent—we have seen eight since October, 1960.

A survey into this condition has recently been conducted by the College of General Practitioners, and the results are being prepared for publication. Notifications have been made of over 400 cases, and clinical records of more than 150 have been collected. From the material it has been possible to calculate a prevalence figure, to demonstrate the geographical distribution of cases in the U.K., and to show the occupations of a large number of sufferers, and the jobs at risk in agriculture.

It has become apparent to us that onset of the disease, though it may be abrupt, as suggested in your article, may also be very insidious, particularly when the source of the illness is hay rather than straw products. A duration of illness above six months is not uncommon in our series.

We would, however, disagree with your statement that "it is on the radiological appearance that the diagnosis usually depends." During the scientific sessions at the Annual General Meeting of the B.M.A., 1960, a paper was read to the joint sections of Chest Diseases and Occupational Health (July 2, 1960, p. 56), reporting that marked deviation from normal function of the lung can coexist with an apparently normal radiograph. This finding has been repeated in a number of cases in our survey series. We would therefore prefer to say that it is on the industrial history, together with the demonstration of impaired lung function, that the diagnosis depends, and that chest radiography, if negative, does not rule out the diagnosis of farmer's lung. Should the radiological appearances be characteristic, then this is useful confirmatory evidence.

We would make a plea for lung-function tests in all cases where this disease is suspected. Simple tests are within the competence of the general practitioner; more sophisticated test equipment is to-day widely available in general hospitals.—We are, etc.,

Callington, Cornwall. F. H. STAINES.
Barnstaple, Devon. J. A. S. FORMAN.

Obstructive Airways Disease

SIR,—In the very interesting account of a patient with progressive respiratory failure (March 25, p. 889), the Hammersmith physicians discuss the finding of a raised serum bicarbonate being caused by a metabolic alkalosis, and this is referred to as a "little point." With great respect to such well-known authorities, I submit that this is no little point, but the whole point round which such a patient's management must revolve. As long as we continue to accept the plasma bicarbonate (CO_2-combining power or alkali reserve) as our guide to acid/base balance, for so long do we deserve to be confused and will our patients be acidified when acidotic and given alkalis when alkalotic.

Singer and Hastings[1] and Astrup *et al.*[2] have described easily measured indices of the metabolic component of acid/base disturbances. The standard bicarbonate does not alter with respiratory disturbances causing large changes in pCO_2, and its adoption into current clinical practice is surely overdue.—I am, etc.,

Southampton General Hospital, Southampton. P. J. HORSEY.

REFERENCES

1 Singer, R. B., and Hastings, A. B., *Medicine*, 1948, **27**, 223.
2 Astrup, P., Jorgensen, K., Andersen, O. S., and Engel, K., *Lancet*, 1960, **1**, 1035.

Prevention of Dental Caries

SIR,—I was very interested to read your sensible and well-balanced leading article (January 28, p. 262) and also Mr. W. Warwick James's suggestion (February 25, p. 593) that the bacteriologist is most likely to help in this matter. I would like to comment on two points—namely, causation and fluoridation.

It is possible that the lactobacilli which Mr. Warwick James and many others have linked with causation do have a rôle to play by virtue of the fact that these bacilli can ferment sugars, resulting in the production of fairly high concentrations of acid in which they can exist, the acid itself perhaps having a deleterious effect on the enamel. To my mind it is more important to consider the factors which encourage the growth of such organisms on and around teeth.

Most members of the genus lactobacillus are microaerophilic or anaerobic, probably because they lack the enzyme catalase. One of the best ways of growing anaerobes in the laboratory is to place them in a medium containing powerful reducing agents. This buffers them from the deleterious action of oxygen and allows them to survive. An environment where good reducing agents are present together with diminished oxygen tension is to be found in the adult vagina, where lactobacilli are normally found in large numbers. Sugar is an article of food which figures very largely in civilized diets. It has been estimated that in the first Elizabethan era the intake was some 4 lb. (1.814 kg.) per head per year, whereas it is now of the order of 100 lb. (45.36 kg.). Sugar is a powerful reducing agent and is presented in a variety of forms, many of which adhere powerfully to structures in the mouth. It is therefore very likely that sugar, coupled with other reducing agents added to food or drink, will encourage lactobacilli to grow and at the same time upset the balance of organisms in the normal healthy mouth.

Lactobacilli and reducing agents in the presence of oxygen can produce hydrogen peroxide. The enzyme catalase which is present in the majority of our cells is

intimately linked with their respiration[1] and their defence mechanisms.[2] It is believed that catalase, although playing a protective role against H_2O_2, has a more important action in utilizing the minute amounts of H_2O_2 produced by living cells for essential purposes.[3] There is probably a specific catalase peroxide balance for each cell; if this is interfered with either by diminution of the catalase or by elevation of the H_2O_2 then abnormalities may occur.[4] Puig Muset[5] has already raised this point in connexion with dental caries. Since lactobacilli can generate H_2O_2 and since a number of catalase poisons (e.g., SO_2, sod. nitrite, H_2S) are taken in with food, drink, or air, the conditions are ideal for tipping the balance in favour of over-oxidation which could, together with the acid produced, result in the degradation of teeth. It has already been suggested that air pollution with SO_2 has a big part to play in dental caries.[6 7]

Your leading article states that there is little doubt that caries can be prevented to a large extent by the elimination of our so-called civilized diet. I agree wholeheartedly with this, but would also couple with it the elimination of the large number of chemical agents (many of which are enzymic poisons) which civilized man has allowed to pollute his food and drink. I do not agree that a reversal of the position is impracticable. Many eminent workers, including the Nobel Prize winners Alexis Carrel[8] and Szent-Györgyi,[9] and more recently René Dubos,[10] have said that until we intelligently reform some of our habits of civilization there will be no measurable reduction in the prevalence of the disease peculiar to our time. In view of the widespread concern both in medical and non-medical circles about the mounting chemical adulteration of air, food, and drink, it is my opinion that the time is ripe for the control of these hazards which have largely replaced the bacterial hazards so prevalent towards the end of the last century.

It is pertinent to consider the advisability of using sodium fluoride. Apart from the ethical side of regularly dosing thousands of people without their consent, and the debatable advantages to be gained by adults, the question of the long-term effects needs much more investigation.

Fluoride is a well-known inhibitor of several enzyme systems. In some respects sodium fluoride acts in the body as a whole like potassium cyanide.[11] This is to be expected, since both fluoride and cyanide can form spectroscopically recognizable compounds with the enzyme catalase,[12] resulting in its inhibition. Catalase poisoning has been linked with the development of viruses[13 14] and the causation of a number of diseases, including cancer.[5] One of the well-established facts about cancer is that as the tumour grows the cells become progressively deficient in catalase and the total body catalase is lowered.[15] Many observers have suggested that agents which decrease the catalase of cells may predispose to tumour formation. Voisin[2] has said, "The method most likely to solve the problem of cancer is to ask why the cancer cell is lacking in catalase and try to prevent this impoverishment taking place." Since fluoride can inhibit catalase and since it is a cumulative poison, the danger of increasing the cancer-inducing potential in humans must be considered. Although there is not to my knowledge any good positive evidence as yet linking fluoride with known cancer cases, the whole question of fluoride intake from food, water, insecticides, and industrial processes should be much more thoroughly investigated.—I am, etc.,

R. A. HOLMAN.

Institute of Pathology,
Royal Infirmary, Cardiff.

REFERENCES

1 Loew, O., *A New Enzyme of General Occurrence with Special Reference to the Tobacco Plant*, 1901. U.S. Department of Agriculture, No. 68.
2 Voisin, A., *Soil, Grass, and Cancer*, 1959. Crosby Lockwood and Son, London.
3 Holman, R. A., *Symposium Internazionale di Medicina ed Igiene Sociale. Atti Ufficiali*, 1957, p. 114. Trieste.
4 —— *Nature (Lond.)*, 1956, **178**, 424.
5 Puig Muset, P., *Los Hidro-Metabólitos y las "Enfermedades de la Civilización,"* 1954. Argos, Barcelona.
6 Pybus, F. C., *Med. Press*, 1959, **241**, 88.
7 Holman, R. A., ibid., 1959, **241**, 155.
8 Carrel, A., *Man, the Unknown*, 1948. Penguin Books, London.
9 Szent-Györgyi, A. V., *On Oxidation, Fermentation, Vitamins, Health, and Disease*, 1939. The Abraham Flexner Lectures Series, No. 6. The Williams and Wilkins Co., Baltimore.
10 Dubos, R., *Mirage of Health*, 1959, p. 134. Allen and Unwin, London.
11 Bond, A. M., and Murray, M. M., *Brit. J. exp. Path.*, 1952, **33**, 168.
12 Baldwin, E., *Dynamic Aspects of Biochemistry*, 3rd ed., 1957, p. 158. Cambridge University Press, London.
13 Yamafuji, K., Yoshihara, F., and Eto, M., *Enzymologia (Hague)*, 1952, **15**, 204.
14 Atanasoff, D., *Genesis of Viruses*, 1959. Government Publishing House Med. 1, Physicultura, Sofia.
15 Greenstein, J. P., *J. Amer. med. Ass.*, 1952, **148**, 697.

Inheritance in Pyloric Stenosis

SIR,—Your reporters do wonderfully well at conferences; but as there is so commonly confusion between sex-linkage and sex-limitation, may I correct the report (April 8, p. 1026) that I said at a recent conference that inheritance in pyloric stenosis was sex-linked. I quoted 11 instances where an affected man had an affected son, and noted that this effectively ruled out sex-linked inheritance; men do not transmit their X chromosomes to their sons. The sex ratio in pyloric stenosis must be attributed to sex-limitation—that is to say, that the genetic predisposition, whatever its nature, manifests itself more readily in boys than girls.—I am, etc.,

Orpington, Kent. C. O. CARTER.

Medicine Broadcast

SIR,—As producer of the B.B.C. Television series "Your Life in Their Hands," I was naturally interested in the comments of your correspondent, Dr. G. D. Jones (March 11, p. 750). It is interesting that out of the many letters received from members of the public the only complaint so far should come from a member of the profession. These programmes have been carefully designed to inform and reassure the uninitiated, and in this we seem to have succeeded, for there is overwhelming evidence—apart from correspondence—of viewers' grateful acceptance of our intentions.

However, the primary object of my writing is to correct a general impression implanted by your correspondent, that these programmes are devised to appeal to the morbidly curious, that they are "dramatized," that they are irresponsibly prepared, and that they represent a "new departure in medical ethics." On his own admission, your correspondent had not seen one of the two subjects he cites—"Open Heart Surgery"—as this programme was not transmitted until March 22. I suspect that neither did he view the "Exchange Transfusion" programme.

In the first place, these programmes are not designed, as your correspondent implies, to advertise the medical profession. This would be a most improper function for the B.B.C. to perform: they are prepared most carefully in consultation with hospital specialists and consultants, who would surely not give up so much of their limited time or devote so much effort if they shared your correspondent's opinions. Nor do they represent a "new departure." In 1958 the B.B.C. presented the first series under this title. It was the enthusiastic welcome afforded by the viewing public to it then that has prompted the current series.

It will probably horrify your correspondent to realize that an average of 10 million people watch each of these programmes. With this in mind, however, is it likely that we, or those eminent members of your profession who collaborate, will be able to accept your correspondent's contention that these programmes aim merely to "Teach Yourself Medicine"?—I am, etc.,

London W.12. W. G. DUNCALF.

Bound Journals for Adelaide

SIR,—The problem of adequately equipping the journal section of a library of a new hospital is most acute in the first years. The Queen Elizabeth Hospital in Adelaide was opened for patients in 1959. It is the second university teaching hospital in the city, and has a total of 500 beds. There is a fine new library, but it has been difficult to acquire bound volumes of back numbers of journals for the shelves.

It is thought that there may be doctors or others among your readers who would like to donate bound volumes of journals covering all or part of the last twenty years. The hospital would be most grateful if prospective donors would write with details to the medical superintendent. Any transport costs for acceptable volumes would be borne by the hospital.—I am, etc.,

R. DOUGLAS CARMAN, Medical Superintendent.

The Queen Elizabeth Hospital, Woodville Road, Woodville, South Australia.

POINTS FROM LETTERS

Top Executives

Mr. H. B. WRIGHT, F.R.C.S., and Dr. ARTHUR LEVIN write: You were good enough to publish a letter from us (June 13, 1959, p. 1531) inviting doctors to co-operate in a long-term investigation into the value of the so-called "top executive" medical examination. Through the courtesy of your columns we obtained a number of valuable contacts. Recent analyses of the first 800 cards showed quite clearly that the investigation was likely to give us the information we wanted, particularly if we could get further collaboration. We have been lucky enough to get considerable participation from America. It should, as a result, be possible to compare the results of the more extensive and frequent American practice with our own more limited approach. We are now anxious to extend participation, and details will gladly be sent to any interested potential participants who write to the Medical Research Unit of the Institute of Directors, 10 Belgrave Square, London S.W.1.

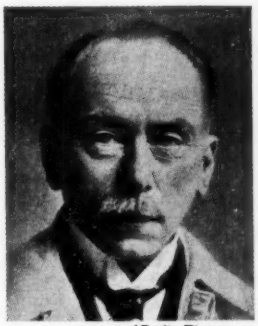
Prevention of Dental Caries

Dr. C. G. DOBBS, Ph.D., Botany-Forestry Building, University College of North Wales, Bangor, writes: On March 3 the Rt. Hon. Enoch Powell, the Minister of Health, addressed a small meeting in Bangor and, in reply to a question from myself, informed those present that the medical aspects were being fully attended to in the Ministry's fluoridation studies. Further questioning elicited the information that the medical "check-up," at least in Anglesey, consisted merely in an invitation to local practitioners to report any unusual morbidity, the implication evidently being that the absence of noticeably unusual morbidity will constitute evidence of "safety." Such a procedure could be relevant only if fluoridation were expected to produce recognizable symptoms, such as skeletal fluorosis in adults, which would indeed be an alarming prospect. But if this is not so the operation becomes pointless, except as propaganda, since, as you stated in your leading article (January 28, p. 262): "No quick results to determine whether harmful effects do occur can be expected from these pilot studies."

Obituary

JULES BORDET, M.D.

Professor Jules Bordet, founder and director of the Pasteur Institute, Brussels, and formerly professor of bacteriology in the University of Brussels, died at his home in Ixelles on April 6 at the age of 90. One of the most eminent of living bacteriologists and immunologists, he had carried out fundamental research on bacteriolysis and bacterial haemolysis, and his name and that of Gengou are associated in particular with the discovery of *Haemophilus pertussis* and with the complement-fixation reaction. A Nobel laureate, Professor Bordet was a Foreign Member of the Royal Society and a Foreign Corresponding Member of the British Medical Association.



[*Radio Times Hulton Picture Library*

Jules J. B. V. Bordet was born on June 13, 1870, in Soignies, Belgium, and graduated M.D. at the University of Brussels in 1892. From 1894 to 1901 he worked at the Pasteur Institute in Paris, but was recalled to Brussels in the latter year to become the first director of the Pasteur Institute in that city. A few years later, in 1907, he was appointed professor of bacteriology in the University of Brussels, a post from which he retired in 1935.

His first work on the properties of the sera of immunized animals and on the phenomenon of bacteriolysis was published in 1895, and three years later he reported his important observations on bacterial haemolysis. He regarded the reactions between antigens and antibodies as colloidal phenomena, a view which simplified the more complex hypotheses of Ehrlich. His work with Gengou on the complement-fixation reaction appeared in 1901 and formed the basis not only for the test for syphilis which Wassermann described in 1906, but also for many other diagnostic tests. With Gengou, also, he was the first to describe (in 1906) the causal organism of whooping-cough. This paper, entitled "Le Microbe de la Coqueluche," was published, like much of his other writings, in the *Annales de l'Institut Pasteur*. The second edition of his major book, *Traité de l'Immunité dans les Maladies Infectieuses*, was published in 1939. Among other subjects on which he made original contributions were the anaerobic culture of bacteria, phagocytosis, blood coagulation, and anaphylaxis. The properties of bacteriophages also interested him, and he was stimulated by d'Herelle's work, first published in 1917, to carry out some investigations in his own laboratory.

A research worker of great ingenuity, he was always ready to put his theories to the experimental test, and the results of his work brought great benefits to mankind. Consequently he received the highest international honours, including the Nobel Prize for medicine and physiology in 1919. Before that he had been awarded the Prix de la Ville, Paris, in 1911, and the Hansen prize and Pasteur medal of the Swedish Medical Society in 1913. The University of Cambridge conferred on him the honorary degree of M.D., and he was elected a Foreign Member of the Royal Society in 1916 and a Foreign Corresponding Member of the B.M.A. in 1939.

Professor Bordet was married and had one son and two daughters.

Sir WILLIAM SAVAGE, M.D., D.P.H.

Sir William Savage, the first county medical officer of Somerset, and one of the foremost members of the public health service in Britain, died on April 6 at the age of 88.

William George Savage was born in London on August 15, 1872. His early education was private, and it was at University College, London, and University College Hospital that he worked as a medical student. He graduated B.Sc. in 1894, and went on to graduate M.B., with honours in medicine and gold medal in forensic medicine, in 1896. He took the D.P.H. in 1897 and proceeded M.D. in the following year. After qualification he held the posts of house-physician and resident pathologist at the Sussex County Hospital. Having returned to University College in 1898 as assistant to the professor of pathology, he became in the following year lecturer in bacteriology and public health in University College, Cardiff. In 1903 he was appointed medical officer of health and public analyst of Colchester, and it was while holding those positions that he wrote his first paper on the bacteriological examination of water supplies. In 1909 he became the first county medical officer of Somerset, and the rest of his professional life was spent in that county, though it was not long before he won an international reputation as one of the foremost workers in preventive medicine.

[Lafayette, Ltd.

Savage's name will be chiefly remembered in association with food-poisoning, and particularly with the investigation of salmonella infections. As early as 1908 he was reporting the isolation from animals of what at that time he called the Gaertner group of bacilli. And it was his early studies on the aetiology of food-poisoning outbreaks that led the Medical Research Council to sponsor investigations by himself and Bruce White into the serology of the salmonella groups and their relationship to food-poisoning. Two Medical Research Council reports within a year (Nos. 91 and 92) firmly established the relationship between the various salmonella types and food-poisoning, and showed that domestic animals and vermin were the main reservoirs of these organisms.

Always a keen advocate of the pasteurization of milk, he wrote a report on milk and the public health in 1912, and two years later his book entitled *The Bacteriological Examination of Food and Water* was published. A year later came a book on rural housing, and in 1920 one on food-poisoning and food infections appeared.

He retained an active interest in all these subjects long after his retirement, and only five years ago he wrote on problems of salmonella food-poisoning in this *Journal*, drawing attention to the fact that there was clear evidence of a marked increase in food-poisoning in Great Britain since the end of the second world war, an increase, he noted, which showed no signs of diminution, but rather of still further increase. He ended his paper with these words: "A pathetic faith in the value of voluntary education is no adequate substitute for control based on education and exhortation with adequate reserve powers of enforcement should the will be lacking to obtain proper hygienic standards."

Retiring from his post as county medical officer in 1937, it was not long before he returned to active public health work in Somerset during the second world war. Savage's contributions to public health were recognized in many ways. He was Milroy lecturer and Mitchell lecturer at the Royal College of Physicians, and he gave the Sedgwick Memorial Lecture in the United States in 1932. President of the Society of Medical Officers of Health in 1935, he was the recipient of the Smith Award of the Royal Institute of Public Health and Hygiene in 1940. He examined in public health for the Universities of London, Wales, and Bristol, and he was knighted on his retirement from the post of county medical officer of Somerset in 1938, and in the same year the University of Bristol conferred on him the degree of M.D. (*honoris causa*). After the second world war he did most useful work as chairman of the Ministry of Food's Catering Trade Working Party.

Sir William Savage was one of the last medical officers of health to succeed in an administrative career while at the same time making highly valuable contributions to bacteriological knowledge. A man of great energy and determination, he remained physically and mentally active in old age. He had many interests, and was president of the Somerset Archaeological Society in 1945.

Sir William Savage married Mary A. M. Wilson in 1900, and they had one son and one daughter. His son, Dr. S. W. Savage, followed his father into the public health service and is county medical officer of Warwickshire.

J. F. D. writes: Between us, Savage and I have been responsible for the health services of Somerset for over 50 years, and perhaps I know better than anyone the greatness of this man.

In his early days Savage, by necessity, was a strong and determined believer in the importance of environmental hygiene as the basis for all measures of public health. The years that passed only strengthened him in this view, and perhaps his knowledge and experience of rural housing, water supplies, and sewerage schemes were unequalled by anyone in the history of public health in this country. This man, with energy, with great precision of mind, and with unfailing tenacity of purpose, built up and tended through many years the structure of the health services in Somerset, and yet, when he retired in 1937, and later came back to his old department to assist me during the war years, never by word or action did he try to influence my direction of affairs. He was always completely loyal, and we became close friends and remained so over the years.

Savage enjoyed life. He worked hard and he played hard. To a late age he loved his tennis, his gardening, and his bathing, not from gentle beaches, but preferably from steep and fearsome rocks.

To those who did not understand him he sometimes appeared brusque, and some of the real greatness of the man may well have been obscured in this way; but always he remained a medical officer of great strength of character, and never was he turned away from any project in which he believed.

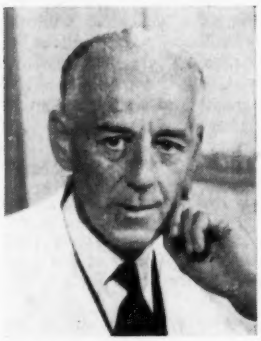
Savage was, indeed, a loyal servant of Somerset, and served the county and her people faithfully through the years. In the county's public health services much will endure as a constant memory of the work of her first medical officer of health.

J. M. SMELLIE, O.B.E., M.D., F.R.C.P.

Professor J. M. Smellie, who was professor emeritus of paediatrics in Birmingham University, died suddenly at his home near Tanworth-in-Arden on Easter Monday, April 3, aged 67. Attacks of ill-health had given cause for anxiety during the past twelve months, but recently his improvement had been encouraging.

James Maclure Smellie was born on May 19, 1893, the son of James Smellie, of Pedmore, Worcestershire. After attending Dumfries Academy, he entered Edinburgh University and graduated M.B., Ch.B. in 1916, proceeding M.D. in 1920. He took the M.R.C.P. of London in 1922 and was elected F.R.C.P. in 1934. In 1947 the degree of M.D. was conferred on him by the University of Birmingham.

In the first world war he served in Salonika with the R.A.M.C., where perhaps he first met Leonard Parsons, his future chief. On demobilization he held resident posts at Edinburgh Royal Infirmary (under Professor Gulland), as resident medical officer at the General Hospital, Birmingham, and as assistant casualty officer at the Hospital for Sick Children, Great Ormond Street. His special interest in children's work led to his election in 1922 as physician to out-patients and pathologist at the Children's Hospital, Birmingham. Shortly afterwards he was appointed assistant physician at the General Hospital. He became lecturer in pharmacology and therapeutics in the university, and for many years he took an active part in the preparation of hospital pharmacopoeias. Until 1939 Smellie was a consultant in Birmingham, practising general medicine with success, and he became well known as a paediatrician. He continued to take an interest in the R.A.M.C. (T.A.), and some recall him as a particularly smart and youthful-looking officer in a field ambulance. After Munich he rejoined the active list and he was appointed officer-in-charge of the medical division of the 14th General Hospital raised from the Birmingham hospitals under (Professor) Colonel Humphrey Humphreys. With this unit he served at Plymouth, at Oxford, in France, in India, and in Burma and Assam. After escaping capture by the Germans in 1940 he and his comrades were surrounded by the Japanese during the serious fighting at Imphal in 1943. Appointed O.B.E. in 1944, he became consulting physician to Eastern Command in India, with the rank of brigadier.



This military experience and his wide knowledge of general medicine and tropical medicine, together with his special study of children's diseases, provided him with a background which stood him in good stead when he returned to civil practice in 1946. Sir Leonard Parsons, the eminent paediatrician at Birmingham, retired from his active hospital practice and teaching in 1946. Smellie was appointed the first whole-time professor of paediatrics and child health at Birmingham University, established under the recommendations of the Goodenough Report (1944). Moreover, with the inception of the National Health Service in 1948, Smellie was fully prepared to provide exactly the qualities of personality and professional skill which were called for. He was an assiduous worker, he gave mature and vigorous direction to his department at the Children's Hospital and as consultant paediatrician at the United Birmingham Hospitals. Further, he was a good lecturer and a friend to colleagues, staff, and patients. Children liked him at sight, and for many years he was Father Christmas at the hospital's Christmas Eve party. With innumerable commitments on committees of the university, hospitals, and other bodies his efficiency became evident to a wide circle. Thus, when he was chairman of the medical committee of the United Birmingham Hospitals, it was remarked that his understanding of problems was expressed in terms of wise judgment, and time was not wasted.

He travelled to the hospitals and universities of many countries of Europe and in America—an addition to his duties which entailed the expenditure of much time and energy. In 1948–9 he was president of the Section of Paediatrics of the Royal Society of Medicine, and in 1958 he was president of the Section of Child Health at the Annual Meeting of the B.M.A. in Birmingham. An original member of the British Paediatric Association—and in 1952–3 its president—he was also a member of the Société de Pédiatrie de Paris. He wrote regularly in journals and textbooks, usually on clinical subjects, but he had no love of writing for writing's sake. In the production of lectures, reports, and even of social letters, conciseness was always a characteristic. One of the last papers he wrote for this journal was a description of the well-known domiciliary nursing service in Birmingham for infants and children.

After retirement from active practice and teaching in 1958, Smellie became professor emeritus, consultant in child health to the Birmingham Regional Hospital Board, and chairman of the Birmingham Area Nurse Training Committee. These activities took up much of his time until a year ago, when serious ill-health caused a check but not a halt. He was elected a life member of the Court of Governors of the University of Birmingham a year ago.

James Smellie was modest and unassuming; he did not struggle for prizes or for the limelight, but his excellent qualities, and in particular his sincerity, became evident to all who worked or played with him. And they soon realized what an able man he was. Ready willingness, an unfailing sense of duty, quickness of perception, and a warm capacity for friendship were attributes which will not soon be forgotten. He was good at games. With a neat figure and a "good eye," he gained colours for hockey at school and Edinburgh, and he played sound golf for many years.

Mrs. Smellie, daughter of the late Harry Lamsdale, and their two sons will receive widespread sympathy from innumerable friends in the loss of a man who played a full part among British doctors both in peace and in war.—H. W. F.

HOWARD C. NAFFZIGER, M.D., M.S.
Hon.F.R.C.S., F.A.C.S.

Dr. Howard C. Naffziger, professor of neurological surgery at the University of California Hospital, San Francisco, from 1947 to 1952, died last month at the age of 74. One of the best-known surgeons on the Pacific coast of the U.S.A., he was an international figure in the neurosurgical world.

Howard Christian Naffziger was born in Nevada City on May 6, 1884, and graduated in medicine at the University of California in 1907. After postgraduate experience at Johns Hopkins Hospital he returned to San Francisco in 1913, joining the staff of the University Hospital and setting up in private surgical practice. During the first world war he served with the American Expeditionary Force, and in the second world war he was one of the American neurosurgeons who visited American Service hospitals in Britain. Appointed clinical professor of surgery in the University of California in 1924, he was professor of surgery and chairman of his department from 1929, to 1947, when he became professor of neurological surgery. He was surgeon-in-chief at the University Hospital for many years.

Dr. Naffziger's published work covered the whole field of neurosurgery, and he was also known for his operation for exophthalmos. He was president of the American College of Surgeons in 1938, and was a member of the editorial boards of *Annals of Surgery* and the *American Journal of Surgery*.

L. C. R. writes: Professor Howard Naffziger was well known in Britain, where he was always a welcome visitor. In July, 1943, the Council of the Royal College of Surgeons of England elected him to its honorary Fellowship, one of the many distinctions which came to him during his lifetime and which indicated the esteem in which he and his work was held. At the time of his death he was professor emeritus in the University of California, while his practice in San Francisco and the west of America had made him the best-known neurosurgeon on the Pacific coast. It would be true also to say he was the best-loved.

The osteoplastic flap designed to have its base in the temporal region and an inconspicuous scar on the forehead, and widely used to expose the frontal lobe of the brain, the pituitary body, or as an approach to a lesion such as a sphenoidal ridge meningioma, though sometimes associated

in this country with the name of the late Wilfred Trotter, is known everywhere in the States as the Naffziger flap. His name is also associated with the operation of orbital decompression for extreme degrees of exophthalmos by removing the orbital plate of the frontal bone through an intracranial approach. Further, he also made a number of important contributions to the surgery of the thoracic-inlet syndrome and costoclavicular compression.

Howard Naffziger was a tall, well-built man with iron-grey hair, rather prominent kind eyes, and a charm of manner which endeared him to his colleagues, his juniors, and his patients—and indeed to all whom he met. His death, coming so soon after that of his friend Geoffrey Jefferson, takes from us two of the most original leaders and high priests of the surgery of the nervous system.

JOHN D'EWART, M.B.

Dr. John D'Ewart, formerly medical superintendent of Booth Hall Children's Hospital, Manchester, died at his home at Manchester on March 28, less than a week before his 89th birthday.

John D'Ewart was, before all else, a Manchester man. Manchester was his home, his school, the scene of his career. He was born in the city on April 3, 1872. He was educated at Owens College, now the Victoria University, and after further training at Dumville Surgical School he qualified in 1902. In his first year he was house-physician at the Royal Infirmary, and afterwards assistant medical officer there and resident medical officer at Crumpsall Infirmary. In 1908 he became assistant school medical officer to the Manchester education committee.

His great work in the service of the Manchester authority was done as medical superintendent of Booth Hall Children's Hospital, then run by the corporation. In the administration of such a hospital he was in his element, and he also took an interest in general hospital questions, as a member of the Hospitals Committee of the British Medical Association and as a prominent member and one-time president of the Medical Superintendents' Society. He made interesting contributions to the literature on epidemic diseases in Manchester, and contributed short papers to this journal from time to time, mostly upon diseases and anomalies found among children. In the early nineteen-twenties he drew the attention of Sir Dawson Williams, then editor of the *British Medical Journal*, to the need for a paediatric journal. His plea that the B.M.A. could sponsor a satisfactory publication fell on receptive ears, and the first number of *Archives of Disease in Childhood* appeared in 1926, to his great delight.

It is many years since John D'Ewart was prominently engaged in central and local activities of the British Medical Association, but many will remember him as a keen debater at Representative Meetings, a lively critic on occasion, and a man who believed with all his heart in the Association and who did everything he could to further its interests. D'Ewart belonged to that not very large company of medical men who have a genius for business, and had they taken up a commercial career would have gone far. He was content to place his business ability at the service of the Association. For some 20 years he was a member of the Finance Committee, a watchdog for economy, but always prepared to agree to wise expenditure in the interests of Association progress. When the B.M.A. moved from the Strand to Tavistock Square in 1925, and the Association was expanding in other directions after the first world war, it was fortunate that its financial affairs at such a time were in the hands of a group of extremely able men, of whom D'Ewart was one, headed by the late Sir Robert Bolam. By their masterly handling of building, finance, and other matters they gave a firm material foundation to the Association, enabling it the better to do the work awaiting it in later years.

Among the medical fraternity of South Lancashire D'Ewart was highly esteemed. He was the joint honorary secretary of the old Lancashire and Cheshire Branch for several years, and chairman of the Manchester Division in 1931–2. He served as the Division's representative at Annual Meetings for 21 consecutive years. He was never on the Central Council, but in addition to his long service on the Finance Committee he gave good service as a member of the Journal and Organization Committees, as well as representative of the Association on the British Medical Bureau. When the Association held its annual meeting at Manchester in 1929 he held the office of honorary local treasurer, and made a magnificent success of the job of collecting and distributing the money. At the Winnipeg Meeting in 1930 he acted as one of the honorary secretaries of the Section of Medical Sociology and History of Medicine, and in 1933 (Dublin) he was vice-president of the Section of Diseases of Children. Outside his professional work one of his great interests was eugenics, and he was lecturer on eugenics and honorary secretary of the Manchester branch of the Eugenics Education Society. Another of his interests was antiquarian lore. Many who knew him in the central work of the B.M.A., and many more in Lancashire, will mourn the passing of a kindly, forthright, public-spirited man, a bit of real Manchester, and a typical "B.M.A. man" in the bargain.

P. S. DAVIS, M.B., B.Chir., M.R.C.P.

Dr. Peter S. Davis, chief assistant in the department of rheumatology at the West London Hospital, died on March 30, aged 38.

Peter Sidney Davis was born on December 1, 1922, and was educated at Oundle and St. John's College, Cambridge, where he rowed for his college in the first May boat. He went on to Westminster Hospital for his clinical training, winning many prizes there. Graduating M.B., B.Chir. in 1946 he filled the posts of house-physician and medical registrar at his teaching hospital, and then became medical registrar in the neurological unit at St. George's Hospital under Mr. Wylie McKissock. He took the M.R.C.P. in 1952 and decided to specialize in rheumatology, becoming senior registrar in the departments of general medicine, rheumatology, and physical medicine at the West London Hospital.

A keen Territorial officer, he held the rank of major (medical specialist).

Dr. W. S. C. COPEMAN writes: The premature death of Dr. Peter Davis, at the age of 38, is a great loss to rheumatology. For the past few years he has been chief assistant to the department of rheumatology at the West London Hospital, where he initiated much valuable clinical research, and also lectured in general medicine in the medical school. He possessed a first-class mind, and would shortly have finalized some original work which would almost certainly have advanced basic knowledge in the field of steroid therapy. He had published several papers jointly on this subject and had recently become particularly interested in the long-term management of rheumatoid arthritis with corticotrophin. He had recently been elected to a committee of the Empire Rheumatism Council, and was honorary secretary designate of the Heberden Society. He leaves a widow and two small sons.

F. D. H. writes: Peter Davis's death is a great loss to all of us who knew him professionally or personally. At Westminster Medical School and Hospital he took most of the prizes in his clinical years; at the inaugural and prize-giving ceremony in his year of qualification (1946) he returned to the rostrum repeatedly for prizes and awards. After working as house-physician and medical registrar at Westminster Hospital he later went to the West London Hospital, where he had worked as senior registrar in the department of rheumatology for some years past, and where he won a considerable reputation as a most reliable clinical and research worker and a man of considerable promise. He had reached that point in his career where, fully trained, he awaited appointment to a consultant post in his chosen specialty. It is a major tragedy that his untimely death should have removed from the medical scene a man of such

obvious talent and great promise. Our deep sympathy goes out to his wife and two children in their tragic loss.

J. D. LEAHY, *M.C.*, M.B., B.Ch.

Air Commodore J. D. Leahy, R.A.F. (ret.), formerly senior medical officer in the Ministry of Transport and Civil Aviation, died suddenly at his home at Sunninghill, Berkshire, on December 10, 1960. He was 67 years of age.

James Daly Leahy received his medical education at Trinity College, Dublin. His studies were interrupted by the first world war, during which he held a commission in the infantry and served in France, Egypt, and Palestine, gaining the Military Cross during his service. On graduating M.B., B.Ch. in 1921, he entered private practice in Ireland, but this was not to his taste and he joined the Royal Air Force, Medical Branch, in April, 1922. Up to the outbreak of the second world war he served as medical officer at home, in India, and in Iraq. On the outbreak of war he went to France as deputy principal medical officer of the Advanced Air Striking Force. In 1941 he was D.P.M.O. at the Cairo headquarters of the R.A.F. in the Middle East, returning to England in 1942 to join the joint planning staff for the invasion of Europe in 1944. When the war ended he commanded Princess Mary's Royal Air Force Hospital at Halton, Bucks, and later was principal medical officer of the Royal Air Force in Occupied Germany. He retired from the Service in October, 1948. He was then appointed a medical officer in the Ministry of Civil Aviation and in two years' time became a senior medical officer. He was retired on September 30, 1960, on the integration of the aviation side of the Ministry of Transport and Civil Aviation with the corresponding side of the Ministry of Supply to form the present Ministry of Aviation. From 1953 to 1957 he was a member of the Armed Forces Committee of the B.M.A.

James Leahy was the very best type of officer and medical man, popular with all he met throughout his service, both military and civil. A fine athlete, he had represented T.C.D. and the R.A.F. at rugby in his time. In India he spent his leave shooting in remote valleys in the Hindu Kush mountains. He learnt to fly with the light aeroplane club at the R.A.F. Station, Karachi, and received serious injuries in an aircraft accident there in 1935. Like many other big men, he was most gentle, kind, and unassuming. From the sound opinions which he reached after careful thought he was not easily moved, and he was able to present his views lucidly and concisely. His knowledge of medicine was extensive and his sound judgment was always available to any who sought it. For the last two years of his life he suffered from ill-health, but by his spirit and determination he concealed it from all except his most intimate friends.

He married in 1946 and is survived by his widow and young daughter.—C. A. L.

HAMILTON BAILEY, F.R.C.S., F.A.C.S.

The obituary of Mr. Hamilton Bailey was published in the *Journal* of April 8 (p. 1043).

Mr. PATRICK CLARKSON writes: Much comment has been made on the curious anomaly that this great surgical teacher had no permanent teaching hospital nor university appointment. But mistakes, even serious mistakes, are inevitable in any system; selection committees are not divinely inspired, thus not infallible; surgeons in the thirties mature, if at all, at different and to unpredictable degrees; guesswork is an irreducible element of these elections. Nevertheless, it is a striking anomaly that the greatest teaching influence of this century (with Mr. McNeill Love) on British undergraduate surgical teaching was from a non-teaching hospital, the Royal Northern. A major element in the success and popularity of this teaching was Mr. Bailey's own success with his (very enlightened) publishers in convincing them that the most expensive production, with top-quality paper and lavish plain and coloured diagrams and photos, would pay, which it did. This top-quality production—ideal for "tired students with tired eyes"—was backed by most clear, fluent, crisp English, and the greatest of practical experience. Its continuing success into the very present, both absolute and comparative to other textbooks of the last 30 years, has been prodigious. This success was not only a tribute to the authors but constitutes a confirmation of the views expressed here about his teaching importance. At a different level—postgraduate, and chiefly affecting young surgeons in training—a special tribute is due to Mr. Bailey's *Emergency Surgery*. Throughout the nineteen-thirties the beneficial effect of this clear, practical, comprehensive, and sound book to the acute surgical sick of Britain was widespread and profound. I belong to the generation of once young surgeons who did surgical locums or semi-permanent jobs early—jobs without supervision appropriate to our lack of experience (most of us would have resented such supervision anyway). Almost universally it was Hamilton Bailey's *Emergency Surgery* to which we turned for guidance in decision before operation on the grave abdomen or other surgical emergencies whose fate was in the balance.

He was a big man physically, as in his influence on surgery. His service in the first world war gave a measure of his quality. I met him briefly for the only time a few months ago, as his luncheon guest at the Authors' Club, to discuss the affairs of the International College of Surgeons, of which he had long been a member and was then the International Vice-President. He was also, of course, an F.R.C.S.(Eng.) and an F.A.C.S. He was anxious to see the work of the I.C.S. prosper all over the world, and repeatedly expressed his view that nowhere should this work conflict, nor in his view had this work ever conflicted, with loyalty of members to their national colleges.

Vital Statistics

Poliomyelitis in Ipswich

In the current outbreak of poliomyelitis in Ipswich there have been 12 cases (10 paralytic) and 2 deaths. The first patient fell ill on February 24. With two exceptions all those affected have been children, and there have been three households with two cases in each. The two fatal cases were a child of 2 and a man of 28. None of the patients had been immunized, and during the past fortnight or so about 10,000 of the population of Ipswich (110,000) have received an injection of vaccine. The evidence suggests a widespread distribution of virus in the town, and a mobile clinic has been set up to assist local doctors in meeting the demand for vaccination.

Scotland in 1960

The high death rate from lung cancer among men is emphasized in the *Report of the Department of Health for Scotland, 1960*, Pt. 1 (H.M.S.O., 5s.). It is described as "a serious and growing problem of public health," and the number of deaths (2,422 for both sexes) was more than twice what it was 10 years ago. The report notes the difficulty of bringing home to young people an understanding of the risks of cigarette smoking against "the high pressure salesmanship directed to the opposite viewpoint." Bronchitis is also a specially prominent cause of death in Scotland, and "progress in setting up clean air zones is likely to do more to bring about improvement than any other single measure."

The proportion of schoolchildren found to be free from defects at routine medical inspections is reported to be increasing. There are great differences in different areas, but "most show a steady reduction in the number of defects" and "the reduction affects almost all types of defect." The heights and weights at given ages have, on the average, increased over the years, but this trend has now

slowed somewhat, so "it may be we are now approaching a stage at which the national average height and weight of the school child is becoming more stable."

The average number of patients on each principal's list in general practice was 1,981, which was 4 fewer than the previous year. "About 79% of doctors have fewer than 2,500 patients on their lists, and it is known that a high proportion of doctors with very large lists employ assistants."

Infectious Diseases

Areas where the numbers of notifications were high in the latest two weeks for which figures are available.

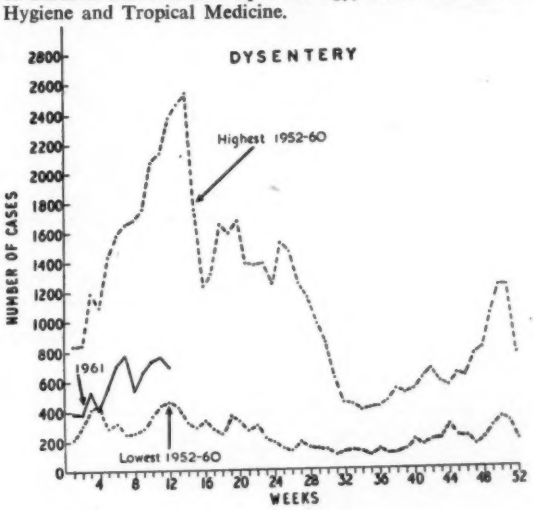
	Week Ending March 25	Week Ending April 1
Measles		
Durham	1,884	**1,448**
Sunderland C.B.	293	**239**
Essex	2,631	**2,607**
West Ham C.B.	247	**277**
Gloucestershire	603	**543**
Bristol C.B.	292	**333**
Hampshire	1,525	**1,329**
Portsmouth C.B.	288	**234**
Southampton C.B.	253	**282**
Lancashire	2,213	**1,888**
Manchester C.B.	320	**228**
Lincolnshire	776	**850**
Grimsby C.B.	234	**416**
London	2,513	**2,517**
Lambeth	238	**193**
Lewisham	200	**207**
Wandsworth	205	**223**
Woolwich	169	**262**
Middlesex	2,386	**2,178**
Harrow M.B.	300	**231**
Northamptonshire	565	**420**
Northampton C.B.	407	**265**
Northumberland	766	**530**
Newcastle upon Tyne C.B.	243	**189**
Staffordshire	1,479	**1,842**
Walsall C.B.	127	**219**
Aldridge U.D.	56	**182**
Surrey	1,547	**1,697**
Croydon C.B.	268	**429**
Warwickshire	2,544	**2,479**
Birmingham C.B.	1,102	**1,177**
Coventry C.B.	557	**344**
Yorkshire East Riding	838	**566**
Kingston upon Hull C.B.	554	**407**
Yorkshire West Riding	2,487	**2,468**
Huddersfield C.B.	131	**434**
Leeds C.B.	291	**337**
Sheffield C.B.	424	**355**
Glamorganshire	1,285	**983**
Cardiff C.B.	556	**506**
Dysentery		
Leicestershire	53	**40**
Leicester C.B.	53	**44**
Yorkshire West Riding	176	**164**
Bradford C.B.	31	**22**
Leeds C.B.	53	**25**
Harrogate M.B.	0	**12**
Thorne R.D.	9	**16**
Paratyphoid fever		
Edinburgh	4	**4**

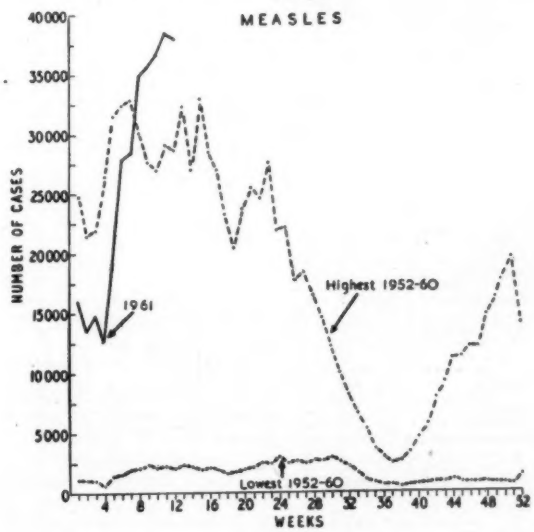
Yellow Fever in Ethiopia

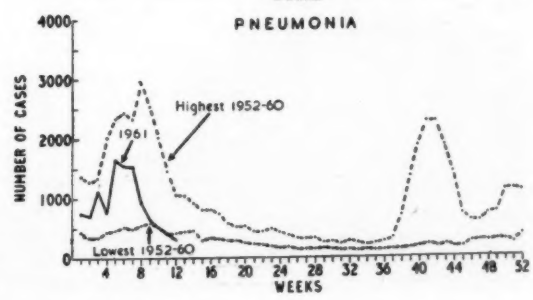
An epidemic of yellow fever in the south-western province of Ethiopia is reported to be moving northwards. The number of fatal cases has been unofficially estimated at 3,000–4,000. A vaccination campaign is under way, and additional supplies of vaccine are awaited. A medical team already in the affected area is reported to have found thousands of monkeys suffering and dying from yellow fever. —*The Times*, April 10, 1961.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1952–60 are shown thus ------, the figures for 1961 thus ———. Except for the curves showing notifications in 1961, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.







INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **March 25** (No. 12) and corresponding week 1960.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	1	0	0	0	3	1	0	3	0	3
Dysentery	694	52	112	7	4	2,067	257	185	20	7
Encephalitis, acute	2	0		0		0	0	0	0	
Enteric fever:										
Typhoid	1	0	0	0		1	1	0	0	
Paratyphoid	5	0	5(B)	1		2	0	2	0	1
Food-poisoning	140	14	4	0		217	26	10	0	
Infective enteritis or diarrhoea under 2 years				15	31				13	20
Measles*	37,993	2513	818	641	466	2,198	83	102	4	29
Meningococcal infection	22	0	3	1	1	21	4	16	1	1
Ophthalmia neonatorum	29	5	3	0		26	3	3	0	
Pneumonia†	302	23	190	7	6	418	17	180	18	5
Poliomyelitis, acute:										
Paralytic	9	0	0	0		2	0	0	0	1
Non-paralytic	2	0				2	1	0		
Puerperal fever§	148	25	13	0		178	37	10	1	1
Scarlet fever	521	30	57	21	16	1,152	43	87	23	29
Tuberculosis:										
Respiratory	414	49	84	12		419	48	54	9	
Non-respiratory	65	1	10	0		50	3	10	3	
Whooping-cough	826	31	56	14	33	903	63	186	4	25

DEATHS	1961					1960				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0	0	0	0	0	0	0	0
Dysentery	0	0		0		1	0		0	
Encephalitis, acute		0			0		1			0
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	4	0	1	0	0	8	0	0	0	0
Influenza	80	6	1	0	3	36	2	0	0	2
Measles	0	0	0	1	1	0	0	0	0	0
Meningococcal infection		2	0				0	0		
Pneumonia	614	43	24	18	9	630	48	30	21	9
Poliomyelitis, acute	1	0		0	0	0	0		0	0
Scarlet fever	0	0	0	0	0	0	0	0	0	0
Tuberculosis:										
Respiratory	60	4	3	0	1	69	2	2	2	4
Non-respiratory		1		0	0		1	0	0	0
Whooping-cough	1	0	0	0	0	2	0	0	0	0
Deaths 0–1 year	331	33	24	6	14	329	29	31	8	11
Deaths (excluding stillbirths)	10,514	856	623	150	204	10,750	821	603	151	193
LIVE BIRTHS	16,448	1322	1091	328	427	16,254	1323	1063	320	404
STILLBIRTHS	306	21	16			314	16	25		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

Wellcome Trust's Third Report

This is the silver jubilee year of the Wellcome Trust, which was established by the will of Sir Henry Wellcome in 1936, and its activities from 1958 to 1960 are charted in the Trust's *Third Report*. During that time the Trustees allocated some £1,200,000. The great increase in the Trust's grant-making activities in recent years can be seen from the fact that in 1959–60 the sum allocated as grants was more than 30 times greater than in 1954–5. Roughly half (£611,800) of the Trust's total benefactions during the period of the report is being used to provide better laboratories for workers with important long-term research programmes in the United Kingdom or overseas, and nearly £163,000 to provide them with items of special research equipment. Many of the grants made during the period have been mentioned in the *Journal*; among those not previously noted is one for providing an Epidemiological Research Unit in Jamaica for the Medical Research Council—which will work in association with the Council's similar unit at Cardiff—at a cost of about £61,000. New awards for research fellowships and expense grants—in such fields as pharmacology, physiology, biochemistry, biophysics, and tropical medicine—amounted to over £98,000; £60,000 over five years was made available to the M.R.C. for the award of Sir Henry Wellcome Travelling Fellowships; 269 Wellcome Research Travel grants were made in 1958–60 at a cost of some £60,000; £20,050 went to assist medical research museums and libraries. The Wellcome Trust's report includes a tribute to Sir HENRY DALE, O.M., F.R.S., who recently retired after 22 years as chairman of the Trust, and a welcome to his successor, Lord PIERCY. The new chairman said this week in London that the Trust was now working to an annual budget of £800,000, a figure which by no means absorbed the entire distributable profits of the Wellcome Foundation Ltd. The Trust hoped in future to play an increasingly useful role in the field of medical research.

Hospital Board Chairmen

The following appointments and reappointments of chairmen of regional hospital boards and boards of governors of teaching hospitals have been made for three years:

Newcastle Regional Hospital Board, Mr. E. F. COLLINGWOOD; *North-east Metropolitan Regional Hospital Board*, Sir GRAHAM ROWLANDSON; *Queen Charlotte's and Chelsea Hospitals*, Mr. G. A. MITCHELL*; *Royal Free Hospital*, the Hon. PETER SAMUEL; *St. Mary's Hospital*, Mr. E. E. LAWLEY; *Hospital for Sick Children*, Mr. C. A. LUCAS; *Bethlem Royal and Maudsley Hospitals*, Mrs F. C. ORMEROD; *Eastman Dental Hospital*, Mr. A. D. PAGE; *United Manchester Hospitals*, Mr. N. M. AGNEW.

*New appointment.

150 Years of Moorfields' Postgraduate Teaching School

An open day was held on April 12 at the Institute of Ophthalmology, London University, and at Moorfields Eye Hospital to mark the 150th anniversary of the founding of Moorfields' postgraduate teaching school (see *B.M.J.*, April 8, p. 1033). There were programmes of televised operations and demonstrations of cases at both branches of Moorfields, and, at the Institute, demonstrations of work being carried out there and a historical exhibition showing the development of some ophthalmic instruments over the past 150 years. In the evening a reception to mark the anniversary was held at the Senate House, University of London.

Ciba Foundation

During 1960, says the Ciba Foundation in its annual report, the Foundation provided accommodation for 825 scientists, including wives, and some on more than one occasion; they came from 37 different countries. Its programme of meetings of various kinds was continued, and it provided facilities for meetings of organizations concerned with cancer, renal function, ageing, world health, reproduction, rheumatism, gastro-enterology, physical therapy,

nutrition, endocrinology, the newborn child, public health, tuberculosis, dental and medical hypnosis, microbiology, medical history, international medical relations, scientific publications, mental health, degenerative diseases, and radiation hazards. Bursaries for work in France were given to seven postgraduate candidates, and two French candidates were welcomed in this country under the same scheme.

Leucotomy Survey

A sample of 10,365 patients who underwent a single leucotomy operation in England and Wales in 1942–54 is the subject of a report from the Ministry of Health last week (*Leucotomy in England and Wales 1942–1954*, by G. C. Tooth, M.D., D.P.M., and Mary P. Newton, M.A.; H.M.S.O., price 2s. 6d.). Of 6,410 patients clinically graded at the time of the survey, 36% of the men and 44% of the women were said to have been at least greatly improved after operation, while 2% of both men and women were worse. But only limited conclusions can be drawn from the survey, for the Chief Medical Officer, Dr. G. E. Godber, writes in the preface: "The results cannot afford a measure of the value of leucotomy, nor are they intended to be used as a basis of comparison with other methods of treatment, particularly by the new drugs now available. They do, however, convey a general idea of what has happened to those patients suffering from different forms of mental derangement who had a leucotomy operation in the period covered by the survey."

New Orthopaedic Appliances Department

A new department of the Manchester Foot Hospital and School of Chiropody—the Orthopaedic Appliances Department—was opened on April 13 by Sir HARRY PLATT. It is believed to be the first time that a building has been constructed especially for the training of students in the use of orthopaedic appliances. At present 28 pupils will use the department during their three-year chiropody training. The department expects to treat 200 patients a month.

Medical Journals for Overseas

The British Supporting Group of the World Medical Association at B.M.A. House has received a very generous response to its scheme for sending journals overseas, and, for the moment, no further copies of the *B.M.J.* are required. A note will be printed in the *Journal* in due course if additional help is needed.

Balderton Hospital

On April 15 the Minister of Health, Mr. ENOCH POWELL, will formally open Balderton Hospital for subnormal and severely subnormal patients.

Originally planned by Nottinghamshire County Council and begun in 1936, building was delayed by the war and the post-war shortage of labour and materials. Under the National Health Service a hospital of 952 beds was designed, and building and reconstruction started in 1953. By the end of 1957 patients were being admitted, and by late 1960 six villas with 252 beds, a hospital unit, patients' workshops, and service and staff units had been completed at a cost of £1,082,383. Since 1953 ideas of what is a suitable size for hospitals of this type have changed, and now only a 150-bed children's unit and a section for low-grade patients of about 180 beds are planned in addition to the 252 villa beds. This stage and a school for the children, to be followed later by a phase covering pavilions, training-units, a recreation hall, nurses' home and training-school, and additional staff accommodation, will bring the total cost of the Balderton Hospital up to almost £2m.

Commonwealth and International Medical Advisory Bureaux

The Commonwealth Medical Advisory Bureau's *Summary of Regulations for Postgraduate Diplomas and of Courses of Instruction in Postgraduate Medicine* has been revised. It contains a new section on nuclear medicine, several courses in this subject now being available to those who are medically qualified. The number of doctors who have used the service of the Commonwealth Medical Advisory Bureau and of the International Medical Advisory Bureau increased during 1960. The greatest number of Commonwealth inquiries came from India, Australia, South Africa, Pakistan, Canada, and New Zealand, in that order, and the largest number of international inquiries from the United States, Spain, U.A.R. (Egypt and Syria), Central and South America, Iran, and Greece, again in that order.

Chair of Orthodontics, University of Glasgow

Mr. T. C. WHITE, whole-time honorary clinical lecturer in orthodontics and head of the orthodontic department, Glasgow Dental Hospital, has been appointed to the university chair of orthodontics.

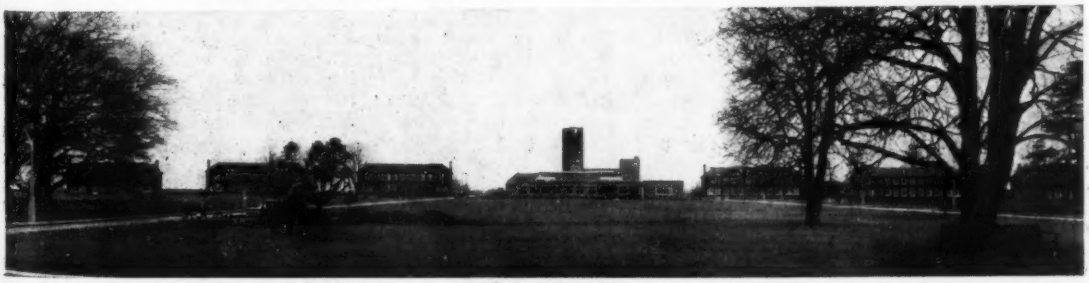
Mr. White qualified L.D.S.(Glas.) in 1933, L.R.F.P.S.(Glas.) and L.R.C.S., L.R.C.P.(Edin.) in 1935. He obtained the Glasgow Diploma in Dental Orthopaedics in 1949. He has practised privately in Glasgow, and in 1938 joined the staff of the Glasgow Dental Hospital and School as part-time lecturer in orthodontics; in 1948 he was appointed consultant dental surgeon, Western Regional Hospital Board. He took up his present posts in 1950. In 1955 he was elected Fellow in dental surgery of the Royal College of Surgeons, Edinburgh, and in 1961 Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow (*qua* surgeon). He has published several articles and was joint author of a textbook, *Orthodontics for Dental Students* (1954), which in 1958 was translated into a Spanish edition.

St. Dunstan's Research Director

Because of the great strides made in electro-mechanics the Council of St. Dunstan's has created a new post, that of director of research. Mr. R. DUFTON, an engineer who lost his sight in an air raid on Plymouth, will be the first to hold it. He will work with the Council's Scientific Committee on projects connected with reading and guiding devices and with the Workshops Development Committee on inventions and gadgets to help the blind, particularly those who are doubly handicapped.

Italian Doctors Strike

Italy's 75,000 doctors have staged a nation-wide 24-hour strike against new income-tax regulations which require them to name all patients and list the fees received from them in their yearly returns instead of making a declaration of gross income. They claim that this will force them to violate professional secrecy (*Sunday Times*, April 9).



Balderton Hospital.

B.M.A. Film Competition

The winners of the B.M.A.'s 1960 competition for 16-mm. medical films were:

Commercial category: Silver Medal, "Resuscitation of the Newborn" (colour, sound, 25 min.), Special Committee on Infant Mortality of the Medical Society of New York and Smith Kline and French Laboratories; Bronze Medal, "Hospital Cross Infection: Dressing Technique in Wards" (colour, sound, 27 min.), Dr. Keith Thompson, Little Bromwich Hospital and Samaritan Films Ltd., for Smith and Nephew Ltd. *Non-commercial category*: Silver Medal, "Claremont"—a documentary film about cerebral palsied children (colour, sound, 12 min.), Bristol Public Health Department and Bristol Amateur Cine Society; Bronze Medal, "The Spitz-Holter Valve in the Treatment of Hydrocephalus" (colour, sound, 20 min.), Mr. R. B. ZACHARY and the Department of Medical Photography, United Sheffield Hospitals.

People in the News

Prince BERTIL of Sweden has bestowed the following decorations on his doctors at the King Edward VII Hospital: Commander of the Order of the Pole Star, Mr. C. N. MORGAN; Knight of the Order of the Pole Star, Dr. E. HERBERT, Dr. J. D. EBSWORTH, and Mr. S. M. COHEN.

Mr. J. BRUCE DEWAR has been appointed chairman and Dr. D. MCKAY HART deputy chairman of the Central Midwives Board for Scotland for the coming year.

Professor C. F. W. ILLINGWORTH has been appointed an honorary surgeon to the Queen in Scotland in the room of Mr. G. G. Bruce, who becomes an extra surgeon there to the Queen.

Dr. W. S. C. COPEMAN will lecture on Tudor medicine at the University of California as exchange Professor of Medical History next spring.

COMING EVENTS

Brook General and Lewisham General Hospitals.—For details of lectures and clinicopathological meetings held on Wednesdays at 5.45 p.m. during April to July see weekly "Societies and Lectures."

Society for the Study of Addiction.—Sir RUSSELL BRAIN, "The Report of the Interdepartmental Committee on Drug Addiction," April 18, 8 p.m., Medical Society of London, 11 Chandos Street, London W.1. Details from Society's Honorary Secretary, 93 Harley Street, London W.1.

Royal College of Physicians.—Exhibition, "The Annals Illustrated" (second series, consisting mainly of 17th- and 18th-century extracts) on view on consultation with Harveian Librarian (WHI 7701) until April 22.

Faculty of History of Medicine and Pharmacy.—Annual general meeting, April 28, 4.30 p.m.; 5 p.m., Gideon de Laune Lecture, Sir GEOFFREY KEYNES, "Timothy Bright," Apothecaries Hall, Black Friars Lane, Queen Victoria Street, London E.C.4.

National Perinatal Mortality Survey.—First results of survey (under auspices of National Birthday Trust Fund) at Royal Society of Medicine, April 28, 5 p.m.

Institute of Diseases of Chest.—Clinical demonstrations open to medical practitioners without fee, arranged by Mr. N. C. OSWALD, in Lecture Room of Institute (in grounds of Brompton Hospital, Fulham Road, London S.W.3), Fridays, 5 p.m., April 28–July 7.

College of General Practitioners (South-west England Faculty).—Symposium, "Emotional Disorders in General Practice," May 6, Torquay, Devon. Details from Dr. W. H. HYLTON, Eglington, Princes Road, Clevedon, Somerset.

University of Clermont-Ferrand (Institut d'Hydrologie et de Climatologie).—International summer course, August 27–September 10. A few scholarships in the form of free accommodation and meals are offered to students of medicine or of pharmacy. Applications should be sent to Monsieur le Directeur des Cours de Vacances, Institut d'Hydrologie et de Climatologie, Faculté de Médecine et de Pharmacie, Boulevard Gergovia, Clermont-Ferrand (Puy-de-Dôme), France.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

ANNALS OF THE RHEUMATIC DISEASES

Heberden Oration. Joseph J. Bunim.
Prevalence of Rheumatoid Arthritis. J. S. Lawrence.
Chloroquine Diphosphate in Rheumatoid Arthritis. A. J. Popert, K. A. E. Meijers, J. Sharp, and F. Bier.
Quantitative and Qualitative Analysis of Joint Stiffness in Normal Subjects and in Patients with Connective Tissue Diseases. Verna Wright and Richard J. Johns.
Spontaneous Atlanto-Axial Dislocation in Ankylosing Spondylitis and Rheumatoid Arthritis. J. Sharp and D. W. Purser.
Experiments with Control Substances. C. R. B. Joyce.
Tissue Mast Cells in the Bone Marrow in Rheumatoid Arthritis. P. C. McCrea.
Corticosteroid Bruising. H. F. West.
University of Toronto Rheumatic Diseases Unit.
Book Review.
British Council.
New Zealand Rheumatism Association.
Abstracts.

Volume 20, No. 1. (Quarterly; £3 annually.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, April 17

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE.—3.30 p.m., Mr. A. G. Cross: Some Common Eye Defects and Ailments (illustrated).

Tuesday, April 18

ILFORD MEDICAL SOCIETY.—At King George Hospital, Ilford, 8.45 p.m., Dr. Richard Asher: Down with Psychosomatic Medicine.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—4.15 p.m., Arnott Demonstration by Dr. A. A. Barton: Replication of Species.
SOCIETY FOR THE STUDY OF ADDICTION.—At Medical Society of London, 8 p.m., Sir Russell Brain, Bt.: Report of the Interdepartmental Committee on Drug Addiction.
WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. K. I. Nissen: Orthopaedic Aspects of Neurological Conditions.

Wednesday, April 19

BONE AND TOOTH SOCIETY.—At 234 Great Portland Street, London W., 5.15 p.m., Dr. Franklin C. McLean (Chicago): Parathyroids and Vitamin D in Calcium Homeostasis.
BROOK GENERAL HOSPITAL.—5.45 p.m., Dr. E. J. Moran Campbell: Breathing and Breathlessness.
HARVEIAN SOCIETY OF LONDON.—At 11 Chandos Street, W., 8.15 p.m., Buckston Browne Prize Essay for 1960: Iatrogenic Disease. An epitome of the winning essay will be delivered by Dr. A. E. Read.
ROYAL FREE HOSPITAL, Gray's Inn Road, London W.C.—5.15 p.m., Dr. Lillian Recant (St. Louis): Concepts of Nephrosis.
SOCIETY OF MEDICAL OFFICERS OF HEALTH: HOME COUNTIES BRANCH.—At Senior Common Room, London School of Hygiene and Tropical Medicine, 2.45 p.m., Presidential Address by Dr. W. Alcock: The Art of Living.

Thursday, April 20

ASSOCIATION FOR THE STUDY OF MEDICAL EDUCATION.—At Royal College of Physicians of London, 5 p.m., Professor J. P. Hubbard: Medical Examining in the U.S.A.
LIVERPOOL SOCIETY OF ANAESTHETISTS.—At Liverpool Medical Institution, 8 p.m., combined meeting with Anaesthetic Section of Manchester Medical Society. Dr. M. Swerdlow: A New Intravenous Anaesthetic; Dr. A. L. Stead: Dental Anaesthesia for Children.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Hunterian Lecture by Professor D. P. Choyce: Development and Uses of All-acrylic Anterior Chamber Implants in Ophthalmic Surgery.

Friday, April 21

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., Mr. S. E. Birdsall: Emergencies in Throat, Nose, and Ear Practice.
SOCIETY OF CHEMICAL INDUSTRY: FINE CHEMICALS GROUP.—At 14 Belgrave Square, London S.W., 6.30 p.m., annual general meeting. 7 p.m., Professor F. Bergel, F.R.S.: Newer Developments in Carcino-chemotherapy.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Fraenkel.—On March 30, 1961, at Dunedin, New Zealand, to Ruth (formerly Anderson), wife of Professor G. J. Fraenkel, a brother for Margaret—David John.
Low.—On March 15, 1961, at Kira-Kira, British Solomon Islands, to Dr. Mary (formerly Tullis), wife of Robin Low, M.A., a son—Christopher David Tullis.

MARRIAGES

Rimmer—McCandless.—On February 28, 1961, at Liverpool, T. B. Rimmer, to Anne E. McCandless, M.D.

DEATHS

Holmes.—On March 25, 1961, at Royal Navy Hospital, Plymouth, Devon, James McAlister Holmes, D.S.O., M.B., F.R.C.S.Ed., Surgeon Captain, R.N., retired, aged 81.
Lees.—On March 14, 1961, at Knutsford, Cheshire, Alfred Everard Lees, M.B., B.S., aged 78.
Murray.—On March 15, 1961, in hospital, Aberdeen, William George Murray, M.B., Ch.B., formerly of Crewe.
Prendiville.—On March 22, 1961, at his home, 183 Bolton Road, Rochdale, Lancs, George Ernest Prendiville, M.B., B.Ch., D.P.H., D.Obst. R.C.O.G.
Prideaux.—On March 22, 1961, at Westbury and District Hospital, Mary Colegrave Prideaux, M.R.C.S. L.R.C.P., of 15 Westbury Road, Warminster, Wilts.
Raffle.—On February 4, 1961, Robert Raffle, M.B., B.S., of 15 Beach Road, South Shields, Co. Durham.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

A Treatment for Disseminated Sclerosis

Q.—*I have heard of a treatment for disseminated sclerosis which aims at "neutralizing" a virus and eliminating toxins with sea-water and seaweed baths. What is this treatment?*

A.—This treatment for disseminated sclerosis is based upon the theory that the disease results from vascular lesions in the central nervous system ("arteritis, endarteritis, and endotheliitis") which in turn are due to rickettsial or viral infection.[1 2] This theory is based upon pathological findings which are described but not illustrated and upon the results of anti-viral and anti-rickettsial agglutination tests carried out upon serum obtained from affected individuals. It is also claimed that the disease can be reproduced in rabbits following upon the introduction of rickettsia into the anterior chamber of the eye, but the experimental evidence given in support of this statement is totally unsatisfactory. According to the author, treatment depends upon "neutralization of the virus, elimination of toxins, stimulation of the cardiovascular system, restoration of the general condition, and the reduction of sequelae." In the author's view these objects can be achieved by means of wide-spectrum antibiotics of the tetracycline group, given in high dosage (2 g. daily), combined with warm sea-water and seaweed baths. The aetiological theories upon which this method of treatment is based lack scientific proof, and the treatment has been administered with no attempt at control. This method is, to the writer at least, totally unconvincing. Unless much more scientific evidence in its favour and in support of the theories of causation upon which it is based is forthcoming, there would seem to be no justification at present for recommending this form of treatment to sufferers.

REFERENCES

1 Le Gac, P., *J. méd. Bordeaux*, 1960, **137**, 346.
2 —— ibid., 1960, **137**, 577.

Oral Hypoglycaemic Drugs and Ketonuria

Q.—*When considering oral hypoglycaemic drugs in the treatment of diabetes, is ketonuria, in the absence of other features of ketosis, a contraindication?*

A.—Provided the ketonuria is due to the diabetic state rather than to other factors, such as an inadequate intake of carbohydrates, then its presence should be regarded as an absolute contraindication to oral hypoglycaemic drugs.

Notifying the Coroner

Q.—*A patient of mine, who had been a coal-miner for 40 years, died at the age of 71. My diagnosis was that he was suffering from chronic bronchitis, emphysema, and cor pulmonale. Should I have signed the death certificate without speaking to the coroner?*

A.—A doctor is under no statutory duty to notify the coroner of the death of one of his patients, except in certain special cases—e.g., when the deceased was in a home for inebriates. The local registrar, to whom the doctor must send the death certificate, is required to notify the coroner when the certificate names certain conditions. These include conditions in which the cause of death appears to the registrar to have been due to industrial disease of the lungs (Registration Consolidated Regulations, 1954, Reg. 82 (1) (g)). In such a case it would be helpful if the doctor notified the coroner directly instead of allowing him to be notified indirectly through the local registrar.

When a doctor has been in attendance upon a deceased person during his last illness the doctor must give a certificate of death, provided he is able to state the cause of death to the best of his knowledge and belief. If he notifies the coroner he should indicate this on the space provided for this purpose on the death certificate.

It is difficult to give an opinion on the attitude a registrar would take to a certificate of death in the terms stated, bearing in mind the fact that the patient was a coal-miner. A death certified as due to pulmonary fibrosis would certainly be notified to the coroner unless accompanied by the words "non-industrial." When a practitioner is satisfied that a death was not due to industrial disease it might be as well to add "non-industrial" after the cause of death, since this would indicate to the registrar that it was unnecessary to report the case to the coroner. Registrars of births and deaths are provided with notes of guidance which contain a list of medical terms in which causes of death due to industrial disease are likely to be certified, but the registrar is informed that it is not necessary to notify the coroner of any such disease which is expressly certified as "non-industrial."

Inheritance of Albinism

Q.—*I have a patient, an albino child aged 3. The child appears to be of normal intelligence but manifests a marked nystagmus. The parents are quite unaware of any such condition in their families. What is the likelihood of further children having this trait?*

A.—Albinism is not associated with any diminution of intelligence. The nystagmus is a result of the absence of retinal pigmentation, as is the photophobia which is one of the principal handicaps. Albinism is transmitted by a recessive gene, only homozygous individuals being affected and heterozygotes escaping. In other words, it is necessary to have two genes for albinism in order to manifest the symptoms. Heterozygotes—that is, individuals carrying a single gene, are fairly common, about 1 in 50 of the population. The chance of two of these marrying and producing a child with the 1 in 4 possibility of being homozygous for albinism is about 1 in 10,000. The risk of further children being affected is 1 in 4 for each pregnancy.

Examining Sperms

Q.—*(1) What is the technique for observing sperm motility? (2) How should sperms be counted, and what is the normal range of sperm counts? (3) If the semen has to be diluted, what diluent should be used and should a stain be used?*

A.—(1) The technique for observing sperm motility is to apply a drop of semen to a cover slip, invert it over a well-slide, so as to produce a hanging drop, and examine with a microscope. Such observation will immediately show whether there is no motility, obviously good motility, or something in between. The objective assessment of this intermediate grade is technically very difficult, and no really satisfactory practical solution has yet been found.

Without going into details about the collection of seminal specimens, it should be emphasized that semen collected in a condom (unless the latter has been well washed and dried before use) invariably contains dead sperms only. Ordinarily, therefore, masturbation specimens are preferred, and the container should be warmed slightly before the semen enters it to avoid "temperature shock."

(2) If the sperm density is low, the count can be made with undiluted semen, using an ordinary haemocytometer chamber. With "normal" semen, dilution with a white-cell pipette must be made, when the counting is done as before. The technique is the same as for counting white blood cells.

Opinions differ on what constitutes "normal" semen. For many years, 60 million per ml. was regarded as a figure below which infertility should be diagnosed, but nowadays

the lower limit for fertility is regarded as something above 20 million per ml., provided volume, motility, and morphology are satisfactory. Many conceptions have been known to occur when the sperm density has been less than 5 million per ml. There is no upper limit to the normal sperm count, but, provided the density exceeds 20 million per ml., mere increase in numbers does not appear to result in enhanced fertility.

(3) Water is a perfectly satisfactory diluent for counting sperms, though, of course, if counts of moving sperms are required, a physiological diluent such as normal saline or Baker's[1] medium must be used, since water immediately kills sperms. Some (e.g., Farris[2]) consider that the total number of moving sperms in the ejaculate provides the best assessment of male fertility. It is not necessary to use a stain for sperm counting, though for observations on sperm morphology stained smears are required.

REFERENCES
1 Baker, J. R., *Quart. J. exp. Physiol.*, 1931, **21**, 139.
2 Farris, E. J., *Human Fertility and Problems of the Male*, 1950. White Plains, N.Y., Author's Press.

Treatment of Hay-fever

Q.—*Antihistamines relieve hay-fever in one of my patients but asthma takes its place. Would desensitization be advisable? Should prednisolone instead of or combined with antihistamines be given in treatment?*

A.—It is presumed that by hay-fever is meant a summer hay-fever. The point is important, because rhinorrhoea and sneezing without any obvious allergic cause may precede asthma. Antihistamines help mild cases of seasonal hay-fever but do not help the associated pollen asthma.[1] Sometimes antihistamines even cause asthma.[2] It is very unlikely that a patient will grow out of a seasonal asthma due to pollen, and therefore an associated asthma is the only definite medical indication for injections in a patient with hay-fever. Injections are given pre-seasonally, and the higher the dose reached the better the result. It may be impossible to reach a reasonably high dosage before the pollen is in the air (in Great Britain) when the injections are not started before April. Steroids in low dosage may be given when all other methods of treating asthma have failed. Rhinitis is usually helped by steroids more effectively than asthma. Antihistamines and steroids can be used together.

REFERENCES
1 Frankland, A. W., and Gorrill, R. H., *Brit. med. J.*, 1953, **1**, 761.
2 Macaulay, D. B., *ibid.*, 1954, **2**, 632.

B.C.G. Concurrently with Other Immunizations

Q.—*Is there any contraindication to carrying out B.C.G. vaccination immediately after or before other immunizations?*

A.—Persons should not be vaccinated with B.C.G. when they are being immunized against other infections. There should be an interval of three weeks between vaccination with B.C.G. and previous or later vaccination against smallpox, yellow fever, or poliomyelitis. B.C.G. may *follow* killed vaccines (other than polio vaccine) a week after they have been given, and it may be *followed* by such vaccines after four weeks. In an emergency, a single other killed vaccine may be given concurrently with, or soon after, B.C.G., provided that the other arm is used. A B.C.G.-vaccinated arm should, if possible, not be used for further vaccinations for three months, because of the possibility of regional lymphadenitis. These recommendations are in accordance with the prevailing British Army instructions.

NOTES AND COMMENTS

Genetic Risks of Radiology.—Dr. J. F. LOUTIT (Radiobiological Research Unit, Harwell) writes: It is not often that I glance at "Any Questions?" but for some reason or other I did in the *Journal* of February 25, and I observed (p. 606), under the heading "Genetic Risks of Radiology," a question: "Is there any chance of a foetal anomaly occurring in a child fathered by a man who has had an intravenous pyelogram performed?" The printed answer to the question is short, sweet, and hopelessly wrong. Firstly, I presume the title is yours. Not all foetal anomalies are, however, genetically determined, but the title is fair enough in that the male parental influence can only be manifested by a genetic mechanism. Nevertheless, the answer should indicate that any woman has a chance of bearing a foetus with an anomaly of non-genetic origin. Thus the chance cannot be nil, whatever the state of the father. Secondly, it depends what the questioner means by foetal anomaly. Everybody (except identical twins) is unique, so who is "normal"? The extreme answer would be nobody except me; but there are generally accepted anomalies which everybody recognizes as such, and these are determined by the genetic constitution. The incidence of these is discussed in the *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation*,[1] and there, from data provided by Dr. A. C. Stevenson (then of Belfast, now of the M.R.C. Population Genetics Research Unit at Oxford), it is shown that about 4% of infants are born with a genetically determined "anomaly." Now whether all these are spontaneous and natural or whether some of them are the direct or indirect result of diagnostic radiology over the past 50 years is, of course, completely unknown. There is no control series I know of from pre-radiological years. To provide the answer to the questioner would take many, many paragraphs and not three lines, but I think the short answer is that, according to the geneticist's calculations, the chances of genetically determined foetal abnormalities occurring in a child fathered by a man who has had an intravenous pyelogram performed are likely to be so small that they could not be measured against the high natural incidence of genetically determined foetal anomalies.

REFERENCE
1 *Report of the United Nations Scientific Committee on the Effects of Atomic Radiation*, 1958. New York.

OUR EXPERT replies: Strictly speaking, Dr. Loutit is correct, although so much is still unknown about human genes that I think the words "likely to be" in his final sentence could well be left out. However, as he says, to provide the answer to the questioner would take many, many paragraphs and not three lines. For this reason, I think my dogmatic answer is the better one.

Injection of Hydatid Cysts.—Dr. G. N. MARANGOS (Nicosia, Cyprus) writes: Referring to the question about the injection of hydatid cysts ("Any Questions?" January 28, p. 307) we also used 10% formol saline for the injection of hydatid cysts and obtained very satisfactory results. However, I disagree with the statement in the last paragraph that the single operation is more dangerous. On account of our experience of many hundreds of cases we have used the one-stage operation for many years with a satisfactory result. Under the cover of antibiotics the cyst is injected with formalin, the content is evacuated, the redundant adventitia is removed, and the cavity is obliterated and closed per primum.

OUR EXPERT replies: It would be interesting and helpful if Dr. Marangos would give further details of his experience with the one-stage operation, as this might well influence current practice in this field. At the present time most would agree that if it is practicable to marsupialize it affords a considerable degree of protection to the patient against contamination of tissue with immature cysts which may ultimately develop into mature cysts.

Correction.—The fourth and fifth lines of the summary of the paper on infertility associated with hirsuties and oligomenorrhoea by Ferriman *et al.* (April 8, p. 1006) should have read "A comparison between the duration of therapy prior to conception . . ." not "contraception."

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